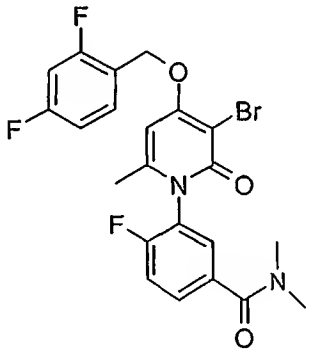
vessel. After stirring at -10 C for 20 minutes, a solution of N-methyl amine (2.1 mL, 4.2 mmol, 2 M in THF) was added and the reaction mixture was warmed to room temperature as it stirred for 18 hours. The reaction mixture was concentrated in vacuo, suspended in water, filtered and washed with water, ethyl acetate and diethyl ether. ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (dddd, J = 3.0, 6.4, 9.2 and 11.6 Hz, 1H), 7.81 (dd, J = 3.0 and (.2 Hz, 1H), 7.66 (q, J = 10.4 Hz, 1H), 7.47 (t, J = 12 Hz, 1H), 7.06 (t, J = 12 Hz, 2H), 6.67 (s, 1H), 5.38 (s, 2H), 2.91 (s, 3H), 2.10 (s, 3H) ppm. ^{19} F NMR (400 MHz, CD_3OD) δ -111.50 (1F), -115.97 (1 F), -120.16 ppm. ES-HRMS m/z 481.0346 (M+H calcd for $C_{21}H_{17}BrF_3N_2O_3$ requires 481.0369).

Example 599

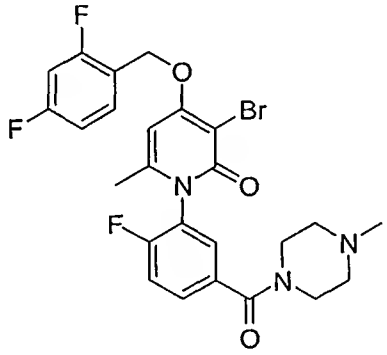


3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N,N-dimethylbenzamide

A solution of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (1 g, 2.1 mmol) in N,N-dimethylformamide (20 mL) was cooled to -10 C. Isobutyl chloroformate (0.27 mL, 2.1 mmol) and N-methyl morpholine (0.23 mL, 2.1 mmol) were added to the reaction vessel. After stirring at -10 C for 20 minutes, a solution of N-methyl amine (2.1 mL, 4.2 mmol, 2 M in THF) was added and the reaction mixture was warmed to room temperature as it

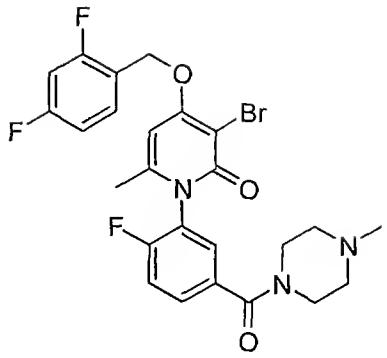
stirred for 18 hours. The reaction mixture was concentrated in vacuo and partitioned between water and ethyl acetate. The organic layer was washed with brine and concentrated in vacuo. The solid was chromatographed on silica (95:5 methylene chloride : isopropyl alcohol) to give the desired product as a white powder (0.31 g, 30 %). ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (m, 1H), 7.50 (dd, J = 2.4 and 7.2 Hz, 1H), 7.45 (t, J = 9.6 Hz, 1H), 7.04 (t, J = 9.2 Hz, 2H), 6.65 (s, 1H), 5.36 (s, 2H), 3.09 (s, 3H), 3.05 (s, 3H), 2.10 (s, 3H) ppm. ^{19} F NMR (400 MHz, CD_3OD) δ -111.51 (1F), -115.88 (1 F), -121.90 (1F) ppm. ES-HRMS m/z 495.0508 (M+H calcd for $C_{22}H_{19}BrF_3N_2O_3$ requires 495.0526).

Example 600



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2-fluoro-5-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-6-methylpyridin-2(1H)-one

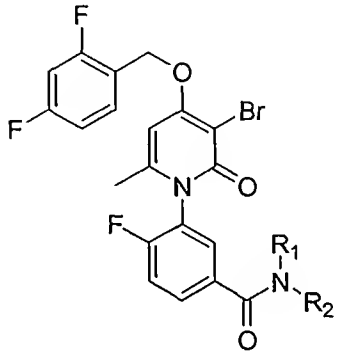
Step 1 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2-fluoro-5-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-6-methylpyridin-2(1H)-one



To a reaction vessel (borosilicate culture tube) was added 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (0.300 g, 0.623 mmol) and 1-hydroxybenzotriazole (0.042 g, 0.45 mmol). N,N-Dimethylformamide (3 mL) was added to the reaction vessel followed by approximately 1.1 g of the polymer bound carbodiimide resin (1.38 mmol/g). Additional N,N-dimethylformamide (2 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. N-Methyl amine (1 mL, 2 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2.0 g of polyamine resin (2.63 mmol/g) and approximately 2.5 g of methylisocyanate functionalized polystyrene (1.5 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours. The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial. After partially evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL). The filtrate was evaporated by blowing N_2 over the vial and the resulting solid was triturated with diethyl ether to give an off-white solid. (0.14g, 41%)

^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (m, 1H), 7.51 (dd, J = 2.2 and 7.2 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H), 7.03 (m, 2H), 6.65 (s, 1H), 5.34 (s, 2H), 3.74 (s, 2H), 3.51 (s, 2H), 2.80 (s, 4H), 2.08 (s, 3H) ppm. ^{19} F NMR (400 MHz, CD_3OD) δ -111.31 (1F), -115.72 (1 F), -121.41 (1 F) ppm. ES-HRMS m/z 550.0946 (M+H calcd for $C_{25}H_{24}ClF_3N_3O_3$ requires 550.0948).

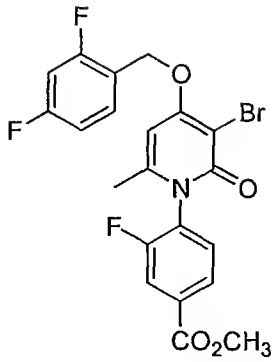
Example 601-603



By following the method of Example 600 and replacing N-methylamine with the appropriate amine, the compounds of Examples 601-603 are prepared.

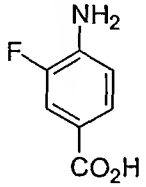
Compound No.	R_1	R_2	% Yield	MF	M+H Requires	ESHRMS m/z
Ex. 601	CH_2CH_2O-	CH_2CH_2-	98	$C_{24}H_{21}BrF_3N_2O_4$	537.0631	537.0620
Ex. 602	CH_3	CH_2CH_2OH	43	$C_{23}H_{21}BrF_3N_2O_4$	525.0631	525.0618
Ex. 603	H	$CH_2C(CH_3)_2OH$	65	$C_{24}H_{23}BrF_3N_2O_4$	539.0783	539.0788

Example 604



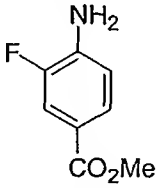
methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-fluorobenzoate

Step 1 Preparation of 4-amino-3-fluorobenzoic acid



3-Fluoro-4-aminobenzoic acid was prepared as described in the literature. (Schmelkes, F.C.; Rubin, M. J. Am. Chem. Soc. 1944, 66, 1631-2.)

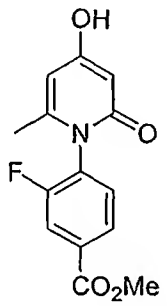
Step 2 Preparation of methyl 4-amino-3-fluorobenzoate



A 250 mL 3-necked round bottomed flask equipped with a nitrogen inlet, stirbar, addition funnel and thermocouple was charged with 4-amino-3-fluorobenzoic acid (11.8 g, 76 mol) and methanol (100 mL). The system was cooled to 0 C and acetyl choride (7.6 mL, 107 mol) was added dropwise. The system was warmed to room temperature, the addition funnel was replaced with a reflux condensor, and was heated to reflux for 6 h. The reaction mixture was cooled to room temperature, quenched

with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic extract was washed with brine and concentrated in vacuo to give methyl methyl 4-amino-3-fluorobenzoate as an tan solid (8.2 g, 64%). ^1H NMR (400 MHz, CD_3OD) δ 7.56 (dd, J = 1.6 and 8.0 Hz, 1H), 7.52 (dd, J = 1.9 and 12 Hz, 1H), 6.76 (t, J = 8.4 Hz, 1H), 3.81 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -139.05 (1F) ppm. ES-HRMS m/z 170.0565 (M+H calcd for $C_8H_9FNO_2$ requires 170.0612).

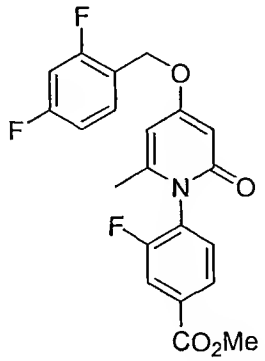
Step 3 Preparation of methyl 3-fluoro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate



A 250 mL round bottomed flask equipped with stirbar, Dean-Stark trap and reflux condensor was charged with the product of Step 2 (8 g, 47.3 mmol), 4-hydroxy-6-methyl-2-pyrone (12 g, 84.6 mmol), and N-methyl-2-pyrrolidine (8 mL). The system was immersed in a 150 C oil bath for 2 hours and was then cooled to room temperature. The reaction mixture was washed with aqueous K_2CO_3 (8.5 g, 200 mL water). The aqueous layer was washed with ethyl acetate and then was acidified to pH 4-5 with glacial HOAc. This was extracted with ethyl acetate, which was then concentrated in vacuo. The viscous oil was triturated with acetonitrile and filtered to the title compound as a tan solid (2.3 g, 17%). ^1H NMR (400 MHz, CD_3OD) δ 7.98 (dd, J = 1.8 and 8.0 Hz, 1H), 7.91 (dd, J = 1.7 and 10 Hz, 1H), 7.46 (t, J = 8Hz, 1H), 6.09 (dd, J = 0.9 and 2.4 Hz, 1H), 5.77 (d, J = 2.7 Hz, 1H), 3.94 (s, 3H), 1.97 (s, 3H) ppm.

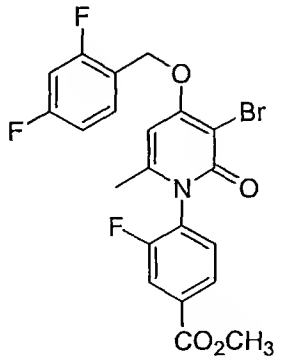
^{19} F NMR (400 MHz, CD_3OD) δ -123.00 (1F) ppm. ES-HRMS m/z 278.0781 (M+H calcd for $C_{14}H_{13}FNO_4$ requires 278.0823).

Step 4 Preparation of methyl 4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-fluorobenzoate



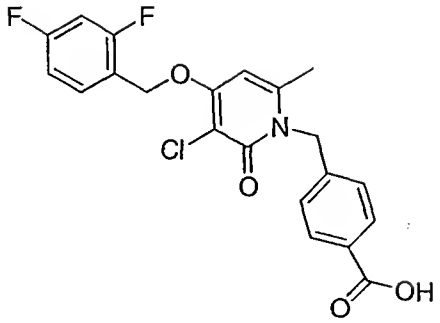
A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 4 (2.3 g, 8.3 mmol) and N,N-dimethyl formamide (20 mL). 1,8-diazabicyclo[5.4.0]undec-7-ene (1.4 mL, 9.1 mmol) was added followed by 2,4-difluorobenzyl bromide (1.2 mL, 9.1 mmol). The reaction mixture was stirred at 60 C for 3 h, was poured into saturated aqueous $NaHCO_3$ and was extracted with ethyl acetate. The organic layer was washed with brine and concentrated in vacuo. The solid was triturated with acetonitrile and filtered to give the title compound (2.15 g, 64%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (dd, J = 1.7 and 8.4 Hz, 1H), 7.93 (dd, J = 1.8 and 10.4 Hz, 1H), 7.55 (m, 1H), 7.48 (t, J = 6.8 Hz, 1H), 7.02 (m, 2H), 6.18 (dd, J = 1.3 and 2.76 Hz, 1H), 6.02 (d, J = 2.7 Hz, 1H), 5.14 (s, 2H), 3.94 (s, 3H), 1.98 (s, 3H) ppm. ^{19} F NMR (400 MHz, CD_3OD) δ -111.34 (1F), -115.97 (1 F), -122.98 (1 F) ppm. ES-HRMS m/z 404.1133 (M+H calcd for $C_{21}H_{17}F_3NO_4$ requires 404.1104).

Step 5 Preparation of methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-fluorobenzoate



A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 4 (2.15 g, 5.3 mmol) and N-methyl-2-pyrrolidine (15 mL). After cooling to 0 C, a solution of N-bromo succinimide (1.03 g, 5.8 mmol) in 10 mL of N-methyl-2-pyrrolidine was added over 15 minutes. After 15 additional minutes, the reaction mixture was warmed to room temperature and was stirred for 1 hour. The mixture was then poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine and concentrated in vacuo. The residue was triturated with acetonitrile and filtered to give the title compound as a white powder (1.5 g, 59%). ^1H NMR (400 MHz, CD_3OD) δ 8.00 (dd, J = 2.0 and 8.4 Hz, 1H), 7.95 (dd, J = 1.7 and 10 Hz, 1H), 7.64 (q, J = 8.8 and 14.4 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.04 (t, J = 8.4 Hz, 2H), 6.66 (s, 1H), 5.36 (s, 2H), 3.95 (s, 3H), 2.01 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.50 (1F), -115.97 (1 F), -123.01 (1 F) ppm. ES-HRMS m/z 484.0169 (M+H calcd for $C_{21}H_{16}BrF_3NO_4$ requires 484.0192).

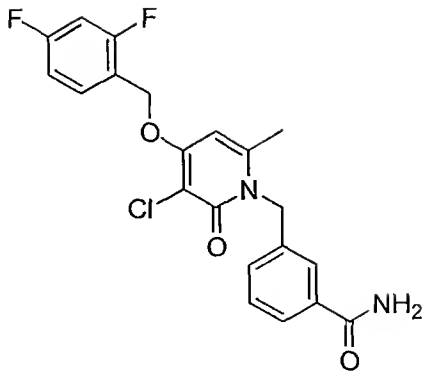
Example 605



4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid:

Preparation of 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid. Methyl-4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate (30.4 g, 70.1 mmol) was suspended in methanol (150 mL) and dioxane (150 mL). 2.5N NaOH (30.8 mL, 77.08 mmol) was added. The resulting mixture was heated to 50 °C for 8.0 hours. The reaction was partially concentrated and the heterogenous mixture was acidified (pH 2) with 1N HCl. The precipitate was collected by filtration washing with H_2O and diethyl ether to afford a white solid (29.2 g, 99 %). ^1H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 8.3 Hz, 2H), 7.63 (app q, J = 7.9 Hz, 1H), 7.31 (dt, J = 2.4, 9.9 Hz, 1H), 7.18 (app d, J = 8.3 Hz, 2H), 7.17-7.12 (m, 1H), 6.60 (s, 1H), 5.35 (s, 2H), 5.27 (s, 2H), 2.28 (s, 3H). ES-HRMS m/z 420.0821 (M+H calcd for $C_{21}H_{17}ClF_2NO_4$ requires 420.0809).

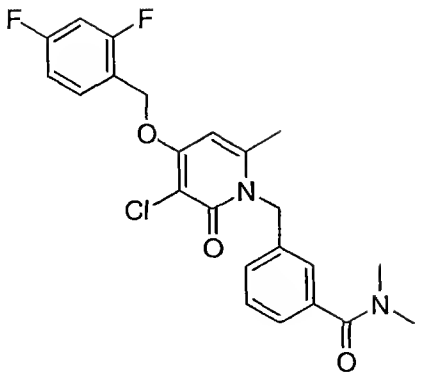
Example 606



4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide

Preparation of 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide. 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid (12.0 g, 28.58 mmol) was suspended in tetrahydrofuran (100 mL). 2-Chloro-4,6-dimethoxy-1,3,5-triazine (6.02 g, 34.3 mmol) was added followed by 4-methylmorpholine (9.43 mL, 85.74 mmol). The resulting mixture was stirred at room temperature for 1.5 hours at which time NH_4OH (50.0 mL) was added. The resulting mixture was stirred at room temperature for 1 hour and then partially concentrated. The precipitate was collected by filtration washing with H_2O and diethyl ether to provide an off-white solid (12.11 g, >100 %). ^1H NMR (400 MHz, DMSO-d_6) δ 7.91 (br s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.63 (app q, J = 7.9 Hz, 1H), 7.31 (dt, J = 2.6, 10.5 Hz, 1H), 7.17-7.12 (m, 1H), 7.13 (app d, J = 8.3 Hz, 2H), 6.59 (s, 1H), 5.32 (s, 2H), 5.27 (s, 2H), 2.28 (s, 3H). ES-HRMS m/z 419.0968 (M+H calcd for $C_{21}H_{18}ClF_2N_2O_3$ requires 419.0969).

Example 607

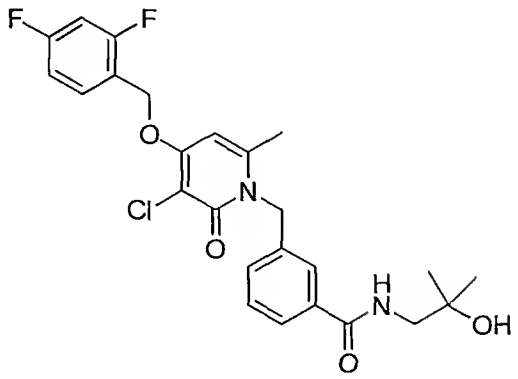


4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylbenzamide

Preparation of 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}}-N,N-dimethylbenzamide. 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid (2.00 g, 4.76 mmol) was suspended in N,N-dimethylformamide (20 mL). 1-Hydroxybenzotriazole (0.773 g, 5.72 mmol) was added followed by 4-methylmorpholine (1.57mL, 14.28 mmol), dimethylamine (7.14 mL, 2.0 M in tetrahydrofuran, 14.28 mmol) and then 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.28 g, 6.66 mmol). The resulting mixture was stirred at room temperature for 3 hours at which time the reaction was diluted with H_2O (75 mL). The reaction mixture was then extracted with ethyl acetate. The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated. The resulting solid was washed with ethyl acetate to provide the title compound as a white solid (1.67 g, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (app q, J = 7.8 Hz, 1H), 7.33 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 6.95-6.90 (m, 1H), 6.84 (app dt, J = 2.5, 9.4 Hz, 1H), 6.02 (s, 1H), 5.35 (s, 2H), 5.19 (s, 2H), 2.97-2.93 (br m, 6H),

2.26 (s, 3H). ES-HRMS m/z 447.1246 (M+H calcd for $C_{23}H_{22}ClF_2N_2O_3$ requires 447.1282).

Example 608

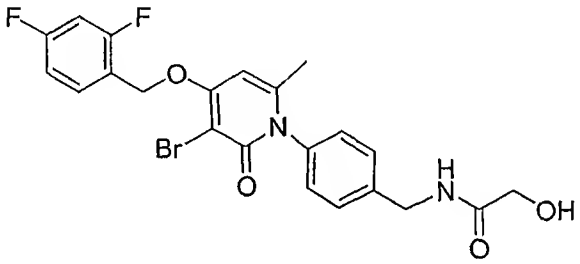


4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzamide

Preparation of 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzamide. 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid (2.00 g, 4.76 mmol) was suspended in N,N-dimethylformamide (10 mL). 1-Hydroxybenzotriazole (0.772 g, 5.71 mmol) was added followed by 4-methylmorpholine (1.57mL, 14.28 mmol), 1-amino-2-methyl-2-propanol hydrochloride (1.49 g, 11.90 mmol) and then 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.28 g, 6.66 mmol). The resulting mixture was stirred at room temperature for 2 days at which time the reaction was diluted with H_2O (50 mL). The reaction mixture was then extracted with ethyl acetate. The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered and

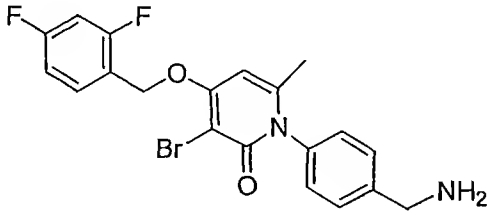
concentrated. The resulting solid was washed with diethyl ether to provide the title compound as a tan solid (2.08 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 2H), 7.51 (app q, J = 7.7 Hz, 1H), 7.25-7.21 (m, 1H), 7.10 (d, J = 8.2 Hz, 2H), 6.93 (app dt, J = 1.6, 8.3, 9.4 Hz, 1H), 6.87-6.82 (m, 1H), 6.01 (s, 1H), 5.32 (s, 2H), 5.19 (s, 2H), 3.42 (d, J = 5.9 Hz, 2H), 2.26 (s, 3H), 1.23 (s, 6H). ES-HRMS m/z 491.1522 (M+H calcd for $C_{25}H_{26}ClF_2N_2O_4$ requires 491.1544).

Example 609



N-{4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}-2-hydroxyacetamide.

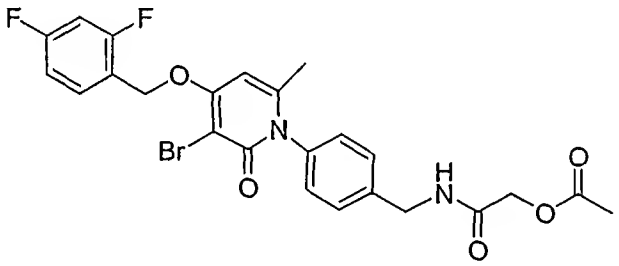
Step 1. Preparation of 1-[4-(aminomethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one.



Example 244 (0.250 g, 0.556 mmol) was suspended in tetrahydrofuran (2.0 mL) and cooled in an ice-bath. Borane dimethyl sulfide (0.500 mL, 2.0 M in tetrahydrofuran, 1.00 mmol) was added. The resulting mixture was heated to reflux overnight and then cooled in an ice-bath. The reaction was quenched by the addition of 6.0 N HCl (5.0 mL) then washed

with ethyl acetate. The aqueous layer was made alkaline with 2.5 N NaOH and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to provide an off-white solid (0.180 g, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (app q, J = 7.8 Hz, 1H), 7.44 (app d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 6.95 (app dt, J = 1.5, 8.5 Hz, 1H), 6.88-6.83 (m, 1H), 6.06 (s, 1H), 5.24 (s, 2H), 3.93 (s, 2H), 1.96 (s, 3H).

Step 2. Preparation of 2-({4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}amino)-2-oxoethyl.

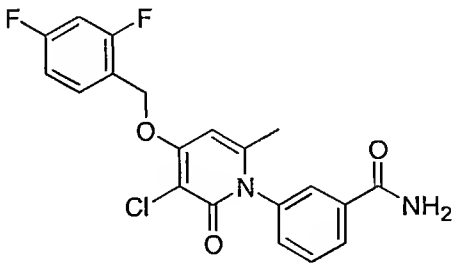


Acetoxyacetic acid (0.037 g, 0.310 mmol) was dissolved in dichloromethane (2.0 mL). 1-hydroxybenzotriazole (0.021 g, 0.155 mmol) was added followed by 3-(1-cyclohexylcarbodiimide)propyl-functionalized silica gel (1.00 g, 0.620 mmol, loading = 0.64 mmol/g). After stirring at room temperature for 15 minutes, 1-[4-(aminomethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (Step 1) (0.180 g, 0.310 mmol) in dichloromethane (2.0 mL) was added. The resulting mixture was stirred at room temperature overnight, at which time the reaction mixture wasfiltered and concentrated. Chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) provided a white solid (0.130 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (app q, J = 7.8 Hz, 1H),

7.33 (d, J = 8.3 Hz, 2H), 7.05 (app d, J = 8.3 Hz, 2H), 6.97-6.92 (m, 1H), 6.88-6.83 (m, 1H), 6.08 (s, 1H), 5.24 (s, 2H), 4.58 (s, 2H), 4.44 (d, J = 6.0 Hz, 2H), 2.13 (s, 3H), 1.95 (s, 3H).

Step 3. Preparation of N-{4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}-2-hydroxyacetamide. 2-({4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}amino)-2-oxoethyl (Step 2) (0.130 g, 0.243 mmol) was dissolved in methanol (5 mL) and H_2O (1 mL). K_2CO_3 (0.055 g, 0.398 mmol) was added and the resulting mixture was stirred at room temperature for 2 hours. The mixture was then concentrated and the residue was partitioned between H_2O and ethyl acetate. The organic layer was removed and the aqueous layer was further extracted with ethyl acetate. The combined organic layer were washed with brine, dried over Na_2SO_4, filtered and concentrated to provide an off-white solid (0.100 g, 84%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (app q, J = 7.7 Hz, 1H), 7.43 (t, J = 5.8 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.04 (app d, J = 8.3 Hz, 2H), 6.98-6.93 (m, 1H), 6.88-6.83 (m, 1H), 6.11 (s, 1H), 5.24 (s, 2H), 4.41 (d, J = 6.0 Hz, 2H), 3.87 (s, 2H), 1.96 (s, 3H). ES-HRMS m/z 493.0575 (M+H calcd for $C_{22}H_{20}BrF_2N_2O_4$ requires 493.0569).

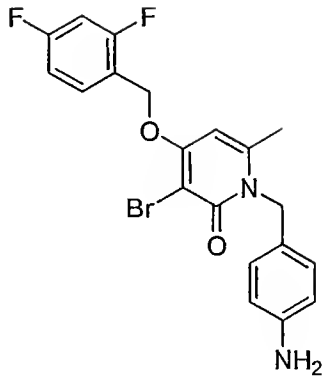
Example 610



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzamide

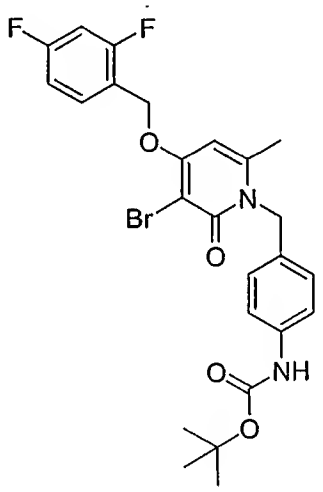
Example 291 (2.00 g, 4.93 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.04 g, 5.91 mmol) were suspended in tetrahydrofuran (20 mL). 4-Methylmorpholine (1.6 mL, 14.79 mmol) was added. The resulting mixture was stirred for 1.5 hours at room temperature. NH_4OH (10 mL, 148.00 mmol) was added and the reaction was stirred for 0.5 hours at room temperature. H_2O (50 mL) and tetrahydrofuran (50 mL) were added and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (75 mL) and the combined organics were washed with saturated Na_2CO_3 (50 mL), 1N HCl (50 mL), and brine (50 mL). The organic phase was dried over Na_2SO_4 and evaporated. The resulting solid was washed with diethyl ether to give a white solid (1.96 g, 98%). ^1H NMR (400 MHz, DMF-d_6) δ 8.24 (br s, 1H), 8.10 (dt, J = 1.21, 7.79 Hz, 1H), 7.90 (t, J = 1.88 Hz, 1H), 7.79 (app dt, J = 6.58, 8.59 Hz, 1H), 7.66 (t, J = 7.79 Hz, 1H), 7.57-7.55 (m, 1H), 7.46 (br s, 1H), 7.33 (ddd, J = 2.55, 9.26, 11.82 Hz, 1H) 7.24-7.19 (m, 1H), 6.78 (s, 1H), 5.44 (s, 2H), 2.04 (s, 3H). ES-HRMS m/z 405.0835 (M+H calcd for $C_{20}H_{16}BrF_2N_2O_3$ requires 405.0812).

Example 611



1-(4-aminobenzyl)-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

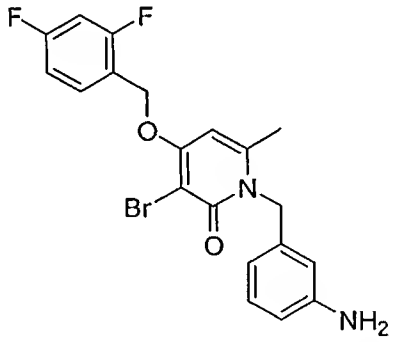
Step 1: Preparation of 1-tert-butyl-4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}phenylcarbamate.



4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid (8.00 g, 17.23 mmol) was suspended in 1:1 acetonitrile:t-butanol (172 mL). Diphenylphosphoryl azide (5.69 g, 20.68 mmol) and triethylamine (2.08 g, 20.68 mmol) were added. The reaction was heated to reflux for 1.5 hours. The reaction mixture was cooled to room temperature, concentrated and subjected to chromatography (on silica, ethyl acetate with 10% methanol/hexanes) to afford an off-white solid (6.14 g, 66%).

Step 2: 1-tert-butyl-4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}phenylcarbamate (Step 1) (6.14 g, 11.47 mmol) was suspended in 4N HCl in dioxane (5.74 mL, 22.94 mmol). The reaction mixture was stirred at room temperature for 1 hour then diluted with diethyl ether. The precipitate was collected by filtration and washed with diethyl ether (3 x 30 mL) to afford a tan solid (3.45 g, 69%). ^{1}H NMR (400 MHz, DMF-d_6) δ 7.64 (app dt, J = 6.58, 8.59 Hz, 1H), 7.31 (ddd, J = 2.55, 9.53, 10.61 Hz, 1H) 7.29-7.12 (m, 5H), 6.56 (s, 1H), 5.28 (s, 2H), 5.27 (s, 2H), 2.28 (s, 3H). ES-HRMS m/z 435.0516 (M+H calcd for $C_{20}H_{18}BrF_2N_2O_2$ requires 435.0514).

Example 612

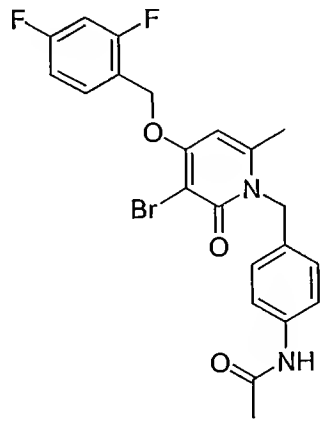


1-(3-aminobenzyl)-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

By following the method for Example 611 and substituting 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid for 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid , the title compound was prepared (2.65 g, 67%). ^{1}H NMR (400 MHz, DMF-d_6) δ 7.64 (app dt, J = 6.58, 8.59 Hz, 1H), 7.39 (t, J = 7.79 Hz, 1H), 7.32 (ddd, J = 2.55,

9.53, 10.61 Hz, 1H) 7.18-7.08 (m, 3H), 6.96 (s, 1H), 6.58 (s, 1H), 5.30 (s, 2H), 5.27 (s, 2H), 2.29 (s, 3H). ES-HRMS m/z 435.0513 (M+H calcd for $C_{20}H_{18}BrF_2N_2O_2$ requires 435.0514).

Example 613

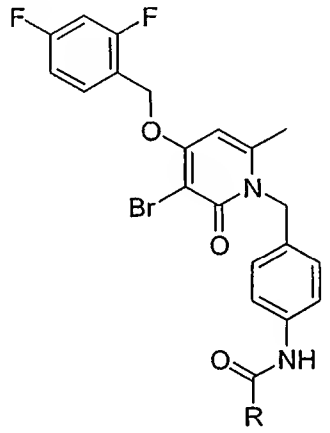


N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}phenyl)acetamide

To a reaction vessel (borosilicate culture tube) was added Example 611 (0.300 g, 0.689 mmol) and dichloromethane (3.0 mL). A stock solution of N-methylmorpholine (0.30 M, 3.0 mL) was added and the parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 10 minutes. Acetyl chloride (0.074 mL, 1.033 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature for 1.5 hours. At this time the reaction was diluted with dichloromethane (15 mL) and treated with approximately 2.1 g of polyamine resin (2.63 mmol/g) and approximately 3.8 g of methylisocyanate functionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature overnight. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts

by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with dichloromethane (2 x 10 mL). The filtrate was evaporated by blowing N_2 over the vial to afford a white solid (0.135 g, 41%). ^1H NMR (400 MHz, DMF-d_6) δ 7.75 (app dt, J = 6.58, 8.59 Hz, 1H), 7.63 (d, J = 8.59 Hz, 1H), 7.30 (ddd, J = 2.55, 9.53, 10.61 Hz, 1H), 7.22-7.14 (m, 3H), 6.60 (s, 1H), 5.37 (s, 4H), 2.40 (s, 3H), 2.06 (s, 3H). ES-HRMS m/z 477.0600 (M+H calcd for $C_{22}H_{21}BrF_2N_2O_3$ requires 477.0620).

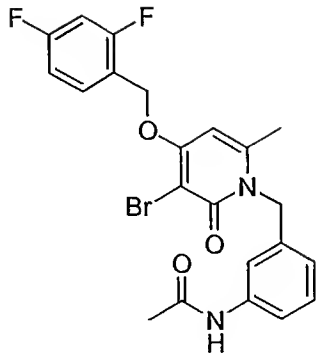
Preparation of Examples 614-616



By following the method for Example 613 and replacing acetyl chloride with the appropriate acid chloride or sulfamoyl chloride, the compounds of Examples 614-616 are prepared. The deprotection of the protected intermediate was accomplished with 1M K_2CO_3 in methanol to afford the title compound.

Compound No.	R	% Yield	MF	M+H Requires	ES-HRMS m/z
Ex. 614	CH_2OH	65	$C_{22}H_{20}BrF_2N_2O_4$	493.0569	493.0593
Ex. 615	CH_2OCOCH_3	43	$C_{24}H_{22}BrF_2N_2O_5$	535.0675	535.0702
Ex. 616	$SO_2N(CH_3)_2$	43	$C_{22}H_{23}BrF_2N_3O_4S$	542.0555	542.0572

Example 617

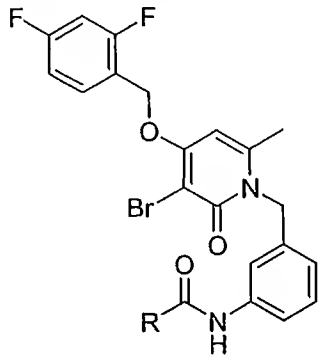


N-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}phenyl)acetamide

To a reaction vessel (borosilicate culture tube) was added Example 612 (0.300 g, 0.689 mmol) and dichloromethane (3.0 mL). A stock solution of N-methylmorpholine (0.30 M, 3.0 mL) was added and the parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 10 minutes. Acetyl chloride (0.074 mL, 1.033 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature for 1.5 hours. At this time the reaction was diluted with dichloromethane (15 mL) and treated with approximately 2.1 g of polyamine resin (2.63 mmol/g) and approximately 3.8 g of methylisocyanate functionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature overnight. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with dichloromethane (2 x 10 mL). The filtrate was evaporated by

blowing N_2 over the vial to afford a white solid (0.167 g, 51%). ^{1}H NMR (400 MHz, DMF-d_6) δ 7.77 (app dt, J = 6.58, 8.59 Hz, 1H), 7.69 (d, J = 8.32 Hz, 1H), 7.41 (br s, 1H), 7.34-7.17 (m, 3H), 6.88 (d, J = 7.65 Hz, 1H), 6.63 (s, 1H), 5.39 (s, 3H), 5.38 (s, 2H), 2.40 (s, 3H), 2.06 (s, 3H). ES-HRMS m/z 477.0620 (M+H calcd for $C_{22}H_{21}BrF_2N_2O_3$ requires 477.0620).

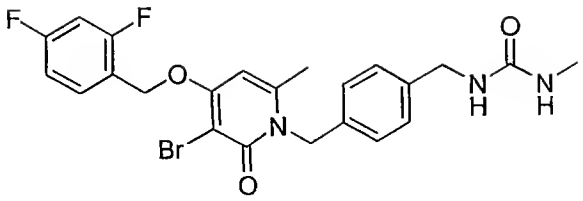
Preparation of Example 618-620



By following the method for Example 617 and replacing acetyl chloride with the appropriate acid chloride or sulfamoyl chloride, the compounds of Examples 618-620 are prepared. The deprotection of the protected intermediate was accomplished with 1M K_2CO_3 in methanol to afford the title compound.

Compound No.	R	% Yield	MF	M+H Requires	ES-HRMS m/z
Ex. 618	CH_2OH	72	$C_{22}H_{20}BrF_2N_2O_4$	493.0569	493.0604
Ex. 619	CH_2OCOCH_3	53	$C_{24}H_{22}BrF_2N_2O_5$	535.0675	535.0692
Ex. 620	$SO_2N(CH_3)_2$	21	$C_{22}H_{23}BrF_2N_3O_4S$	542.0555	542.0567

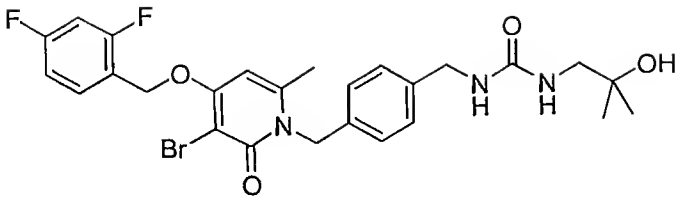
Example 621



N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N'-methylurea

Preparation of (4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N'-methylurea. EXAMPLE 159 (150 mg, 0.33 mmol) was dissolved in N,N-dimethylacetamide (5 mL) and cooled to 0° C. 4-Nitrophenyl chloroformate (100 mg, 0.5 mmol) was added, followed by N,N-diisopropylethylamine (0.15 mL, 0.85 mmol) and the reaction was stirred at 0° C for 5 minutes. N-Methylamine (0.5 mL, 1.0 mmol, 2M in tetrahydrofuran) was added and the reaction was allowed to reach ambient temperature and stirred for 1 hour. The reaction was then diluted with tetrahydrofuran (40 mL) and polyamine resin (1.3 g, 2.81 mmol/g) and methylisocyanate functionalized polystyrene (1 g, 1.38 mmol/g) were added. The mixture was shaken for 16 hours at ambient temperature, filtered, and the resulting filtrate concentrated to an oil that was triturated with ether. The resulting white solid was collected, washed with ether, and dried (87 mg, 52%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (app q, J = 8.4 Hz, 1H); 7.24 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 7.02 (app t, J = 8.4 Hz, 2 H), 6.47 (s, 1H), 5.39 (s, 2H), 5.28 (s, 2H), 4.26 (s, 2H); 2.68 (s, 3H); 2.34 (s, 3H). ES-HRMS m/z 506.0862 (M+H calcd for $C_{23}H_{23}BrF_2N_3O_3$ requires 506.0885).

Example 622

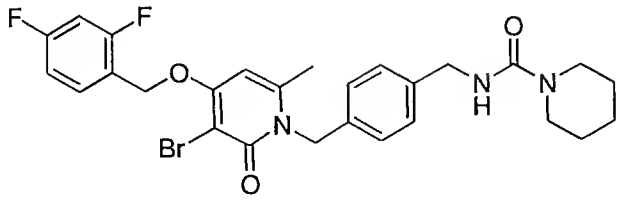


N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N'-(2-hydroxy-2-methylpropyl)urea

Preparation of N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N'-(2-hydroxy-2-methylpropyl)urea. EXAMPLE 159 (300 mg, 0.67 mmol) was dissolved in N,N-dimethylacetamide (5 mL) and cooled to 0° C. 4-Nitrophenyl chloroformate (200 mg, 1.0 mmol) was added, followed by N,N-diisopropylethylamine (0.3 mL, 1.7 mmol) and the reaction was stirred at 0° C for 5 minutes. 3-Amino-2-methyl-2-propanol (248 mg, 2.0 mmol) was added and the reaction was allowed to reach ambient temperature and stirred for 3 h. The reaction was then diluted with tetrahydrofuran (40 mL) and polyamine resin (1.3 g, 2.81 mmol/g) and methylisocyanate functionalized polystyrene (1 g, 1.38 mmol/g) were added. The mixture was shaken for 16 hours at ambient temperature, filtered, and the resulting filtrate concentrated to an oil that was triturated with ether. The resulting white solid was purified by chromatography (silica gel, hexane/ethyl acetate/methanol) followed by reversed phase chromatography (C_{18}, 0.1% aqueous trifluoroacetic acid/acetonitrile) to yield an off-white solid (43 mg, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (app q, J = 8.0 Hz, 1H); 7.12 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 7.02 (app dt, J = 1.6, 8.0 Hz, 2H), 6.83-6.88 (m, 1H), 6.06 (s, 1H), 5.26 (s, 2H), 5.21 (s, 2H); 4.22 (s, 2H); 3.09 (s, 2H); 2.30 (s, 3H);

1.14 (s, 6H). ES-HRMS m/z 564.1279 (M+H calcd for $C_{26}H_{29}BrF_2N_3O_4$ requires 564.1304).

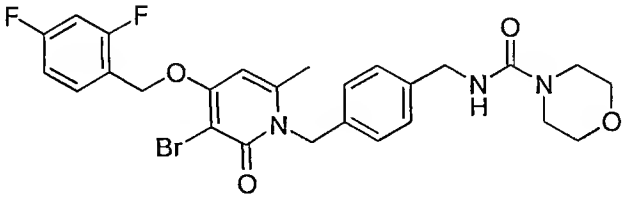
Example 623



N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)piperidine-1-carboxamide

By following the general method for Example 622 and substituting piperidine (170 mg, 2.0 mmol) for 3-amino-2-methyl-2-propanol the title compound was prepared and purified by chromatography (silica gel, hexane/ethyl acetate/methanol) yielding an oil that was triturated with ether to afford a white solid (107 mg, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (app q, J = 8.0 Hz, 1H); 7.23 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.02 (app t, J = 8.0 Hz, 2H), 6.81-6.88 (m, 1H), 5.97 (s, 1H), 5.32 (s, 2H), 5.19 (s, 2H); 4.37 (s, 2H); 3.34-3.28 (m, 4H); 2.29 (s, 3H); 1.68-1.50 (m, 6H). ES-HRMS m/z 560.1365 (M+H calcd for $C_{27}H_{29}BrF_2N_3O_3$ requires 560.1355).

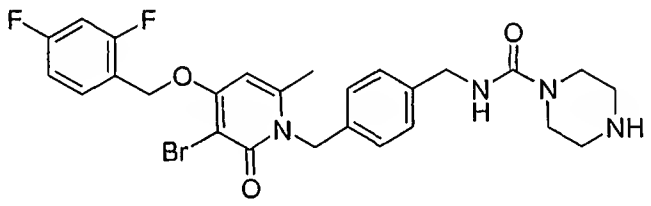
Example 624



N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)morpholine-4-carboxamide

By following the general method for Example 622 and substituting morpholine (175 mg, 2.0 mmol) for 3-amino-2-methyl-2-propanol the title compound was prepared and purified by chromatography (silica gel, hexane/ethyl acetate/methanol) followed by reversed phase chromatography (C_{18}, 0.1% aqueous trifluoroacetic acid/acetonitrile) to yield an off-white solid (51 mg, 13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (app q, J = 8.0 Hz, 1H); 7.17 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.0 Hz, 2H), 6.94(app dt, J = 2.4, 8.0 Hz, 2H), 6.82-6.87 (m, 1H), 6.02 (s, 1H), 5.27 (s, 2H), 5.19 (s, 2H); 4.33 (s, 2H); 3.65-3.62 (m, 4H); 3.34-3.36 (m, 4H); 2.28 (s, 3H). ES-HRMS m/z 562.1152 (M+H calcd for $C_{26}H_{27}BrF_2N_3O_4$ requires 562.1148).

Example 625

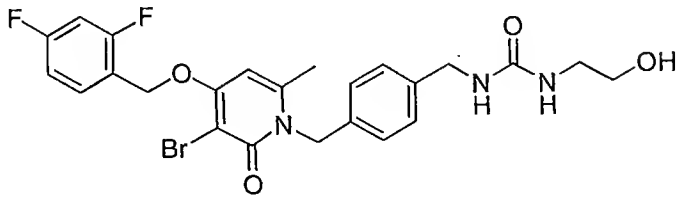


N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)piperazine-1-carboxamide hydrochloride

By following the general method for Example 622 and substituting 1-Boc-piperazine (372 mg, 2.0 mmol) for 3-amino-2-methyl-2-propanol the title compound was prepared from its N-t-butoxycarbonyl protected intermediate that was purified by chromatography (silica gel, hexane/ethyl acetate/methanol). Deprotection was accomplished with 4N HCl in dioxane to afford the title compound as its hydrochloride salt (78 mg, 19%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (app q, J = 7.6 Hz, 1H); 7.26 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.08-7.00 (m, 2H), 6.48 (s, 1H), 5.41 (s, 2H), 5.28 (s, 2H); 4.31 (s, 2H); 3.65-

3.62 (m, 4H); 3.21-3.17 (m, 4H); 2.35 (s, 3H). ES-HRMS m/z 561.1318 (M+H calcd for $C_{26}H_{28}BrF_2N_4O_3$ requires 561.1307).

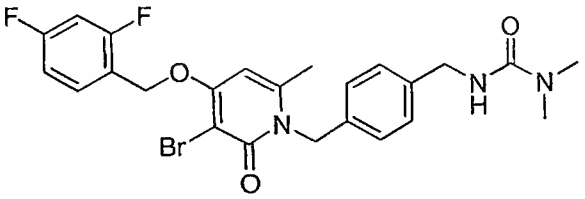
Example 626



N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N'-(2-hydroxyethyl)urea

By following the general method for Example 622 and substituting ethanolamine (121 mg, 2.0 mmol) for 3-amino-2-methyl-2-propanol the title compound was prepared and purified by chromatography (silica gel, hexane/ethyl acetate/methanol) to yield an off-white solid (130 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (app q, J = 7.6 Hz, 1H); 7.13 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 6.96-6.92 (m, 1H); 6.83-6.88 (m, 1H), 6.09 (s, 1H), 5.26 (s, 2H), 5.21 (s, 2H); 4.24 (s, 2H); 3.56 (t, J = 4.8 Hz, 2H); 3.21 (t, J = 4.8 Hz, 2H); 2.31 (s, 3H). ES-HRMS m/z 536.0948 (M+H calcd for $C_{24}H_{25}BrF_2N_3O_4$ requires 536.0991).

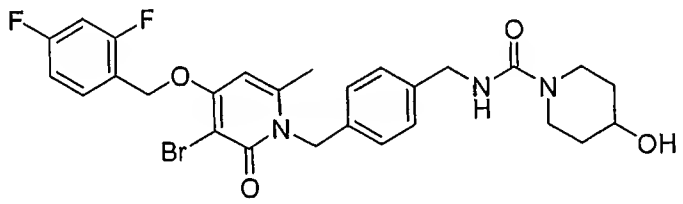
Example 627



N'-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N,N-dimethylurea

By following the general method for Example 622 and substituting N,N-dimethylamine (1.0 mL, 2.0 mmol, 2M in tetrahydrofuran) for 3-amino-2-methyl-2-propanol the title compound was prepared and purified by chromatography (silica gel, hexane/ethyl acetate/methanol) yielding an oil that was triturated with ether to afford a white solid (65 mg, 19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (app q, J = 8.0 Hz, 1H); 7.22 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.93 (app dt, J = 2.0, 8.0 Hz, 1H); 6.87-6.81 (m, 1H); 5.97 (s, 1H), 5.31 (s, 2H), 5.19 (s, 2H); 4.36 (s, 2H); 2.89 (s, 6H); 2.28 (s, 3H). ES-HRMS m/z 520.1072 (M+H calcd for $C_{24}H_{25}BrF_2N_3O_3$ requires 520.1042).

Example 628

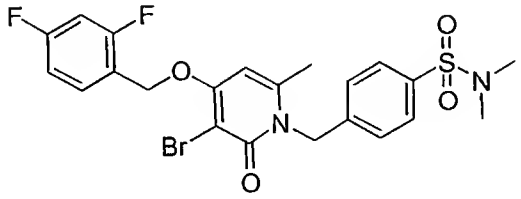


N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-4-hydroxypiperidine-1-carboxamide

By following the general method for Example 622 and substituting 4-Hydroxypiperidine (202 mg, 2.0 mmol) for 3-amino-2-methyl-2-propanol the title compound was prepared and purified by chromatography (silica gel, hexane/ethyl acetate/methanol) yielding an oil that was triturated with ether to afford a white solid (41 mg, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (app q, J = 8.0 Hz, 1H); 7.20 (d, J = 7.6 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.94 (app t, J = 8.0 Hz, 1H); 6.84 (app t, J = 8.0 Hz, 1H); 5.99 (s, 1H), 5.29 (s, 2H), 5.19 (s, 2H); 4.34 (s, 2H); 3.84-3.70 (m, 3H); 3.04-2.92 (m, 3H);

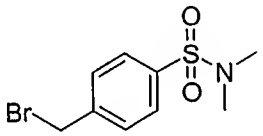
2.28 (s, 3H); 1.84-1.81 (m, 2H); 1.47-1.44 (m, 2H). ES-HRMS m/z 576.1348 (M+H calcd for $C_{27}H_{29}BrF_2N_3O_4$ requires 576.1304).

Example 629



4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylbenzenesulfonamide

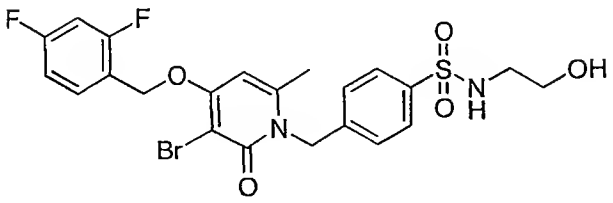
Step 1: Preparation of 4-Bromomethyl-N,N-dimethylbenzenesulfonamide



4-(Bromomethyl)benzenesulfonyl chloride (5.0 g, 18.6 mmol) was dissolved in tetrahydrofuran. N,N-dimethylamine (7.7 mL, 15.5 mmol, 2M in tetrahydrofuran) and and N,N-diisopropylethylamine (3.5 mL, 20.1 mmol) were added, and the reaction was allowed to stir at ambient temperature for 2 hours. The reaction was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried over Na_2SO_4, and filtered. The resulting filtrate was concentrated to an oil which deposited needles that were a mixture of the title compound and 4-chloromethyl N,N-dimethylbenzenesulfonamide The resulting needles were collected and dried (2.3 g, 44 %). ES-MS m/z 534 (M+H) and 578 (M+H).

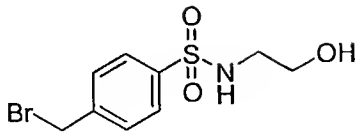
Step 2: Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylbenzenesulfonamide . 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1H)-one (300 mg, 0.91 mmol) was suspended in 1,4-dioxane (50 mL). 4-(Bromomethyl)-N,N-dimethylbenzenesulfonamide (from step1) (300 mg, 1.09 mmol) was added followed by sodium hydride (45 mg, 1.09 mmol, 60% in mineral oil). The reaction was heated to 80°C and stirred for 16 hours after which more sodium hydride (45 mg, 1.09 mmol, 60% in mineral oil) and sodium iodide (150 mg, 1.0 mmol) were added. The reaction was allowed to stir at 80°C for 4 hours more. The reaction was then filtered through Celite® and the filtrate was concentrated to an oil that was purified by chromatography (silica gel, hexane/ethyl acetate) followed by reversed phase chromatography (C_{18}, 0.1% aqueous trifluoroacetic acid/acetonitrile) to yield an off-white solid (41 mg, 8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71(d, J = 8.4 Hz, 2H); 7.57 (app q, J = 7.6 Hz, 1H); 7.29 (d, J = 8.0 Hz, 2H); 6.95 (app dt, J = 2.0, 8.0 Hz, 1H), 6.88-6.83 (m, 1H); 6.05 (s, 1H), 5.42 (s, 2H), 5.22 (s, 2H); 2.69 (s, 6H); 2.29 (s, 3H). ES-HRMS m/z 527.0439 (M+H calcd for $C_{22}H_{22}Br_2F_2N_2O_4S$ requires 527.0446).

Example 630



4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)benzenesulfonamide

Step 1: Preparation of 4-Bromomethyl-N-(2-hydroxyethyl)benzenesulfonamide

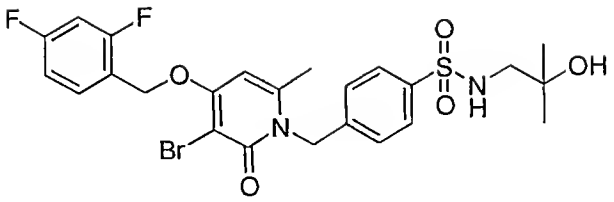


4-(Bromomethyl)benzenesulfonyl chloride (5.0 g, 18.6 mmol) was dissolved in tetrahydrofuran. Ethanolamine (1.1 mL, 18.6 mmol) and and N,N-diisopropylethylamine (3.9 mL, 22.3 mmol) were added, and the reaction was allowed to stir at ambient temperature for 30 minutes. The reaction was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried over Na_2SO_4, and filtered. The resulting filtrate was concentrated to an oil that was a mixture of the title compound and 4-chloromethyl N-(2-hydroxyethyl)benzenesulfonamide. The resulting oil was dried in vacuo (3.7 g, 68 %). ES-MS m/z 250 (M+H) and 294 (M+H).

Step 2: Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)benzenesulfonamide.

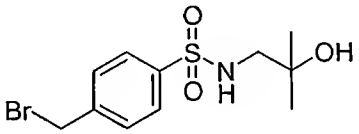
The title compound was prepared essentially according to the procedure described in Step 2 of Example 629, using 4-Bromomethyl-N-(2-hydroxyethyl) benzenesulfonamide (from step 1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 2H); 7.61 (app q, J = 7.6 Hz, 1H); 7.30 (d, J = 8.4 Hz, 2H); 6.95 (app t, J = 8.4 Hz, 2H), 6.53 (s, 1H), 5.49 (s, 2H), 5.30 (s, 2H); 3.50 (t, J = 6.0 Hz, 2H); 2.92 (t, J = 6.0 Hz, 2H); 2.36 (s, 3H). ES-HRMS m/z 543.0453 (M+H calcd for $C_{22}H_{22}Br_2F_2N_2O_5S$ requires 543.0395).

Example 631



4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzenesulfonamide

Step 1: Preparation of 4-Bromomethyl-N-(2-hydroxy-2-methylpropyl) benzenesulfonamide



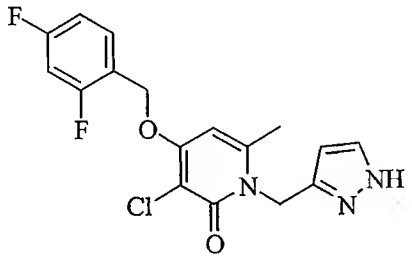
4-(Bromomethyl)benzenesulfonyl chloride (2.0 g, 7.3 mmol) was dissolved in tetrahydrofuran. 3-Amino-2-methyl-2-propanol (1.0 g, 8 mmol) and and N,N-diisopropylethylamine (1.5 mL, 8.8 mmol) were added, and the reaction was allowed to stir at ambient temperature for 30 minutes. The reaction was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried over Na_2SO_4, and filtered. The resulting filtrate was concentrated to an oil that was a mixture of the title compound and 4-chloromethyl-N-(2-hydroxy-2-methylpropyl) benzenesulfonamide. The resulting oil was dried in vacuo (1.9 g, 81 %).

Step 2: Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzenesulfonamide

The title compound was prepared essentially according to the procedure described in Step 2 of Example 629, using 4-Bromomethyl-N-(2-hydroxy-2-methylpropyl) benzenesulfonamide (

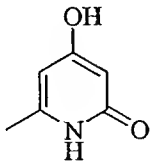
from step 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.4 Hz, 2H); 7.56 (app q, J = 7.6 Hz, 1H); 7.26 (d, J = 8.4 Hz); 6.95 (app t, J = 8.4 Hz, 1H), 6.86-6.83 (m, 1H); 6.07 (s, 1H), 5.41 (s, 2H), 5.22 (s, 2H); 4.98 (t, J = 6.4 Hz, 1H); 2.84 (d, J = 6.4 Hz, 2H); 2.29 (s, 3H); 1.21 (s, 6H). ES-HRMS m/z 571.0684 (M+H calcd for $C_{24}H_{26}Br_2F_2N_2O_5S$ requires 571.0708).

Example 632



3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1-(1*H*-pyrazol-3-ylmethyl)-1*H*-pyridin-2-one

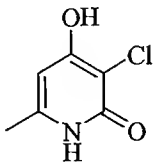
Step 1. Preparation of 4-Hydroxy-6-methyl-1*H*-pyridin-2-one.



4-Hydroxy-6-methyl-pryan-2-one (25.8 g, 0.2 mol) was dissolved in 180 ml of concentrated ammonium hydroxide. The reaction was heated at refluxed for 4 hours. The reaction was cooled to room temperature and evaporated on a rotary evaporator to a quarter of the original volume. The resulting solid was filtered, washed with cold water, hexanes, and dried in a vacuum oven overnight to give a white solid (25 g, 98%): ^{1}H NMR

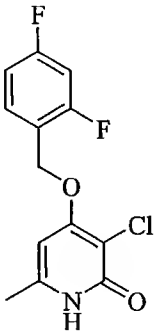
(300 MHz, DMSO-d_6) δ 10.94 (br s, 1H), 10.34 (s, 1H), 5.59 (d, J = 1.4 Hz, 1H), 5.32 (d, J = 2.0 Hz, 1H), 2.07 (s, 3H).

Step 2. Preparation of 3-Chloro-4-hydroxy-6-methyl-1*H*-pyridin-2-one.



4-Hydroxy-6-methyl-1*H*-pyridin-2-one (25g, 0.2 mol) and *N*-chlorosuccinimide (29.4 g, 0.22 mol) were dissolved in 200 mL of acetic acid. The reaction was heated at 115 °C for 6 hours. The reaction was cooled to room temperature, the solid was filtered, and washed with acetic acid and hexanes. The solid was dried in a vacuum oven overnight to give a white solid (19.2 g, 60%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.46 (br s, 1H), 11.04 (s, 1H), 5.79 (s, 1H), 2.09 (s, 3H).

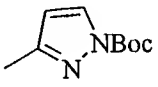
Step 3. Preparation of 3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1*H*-pyridin-2-one.



3-Chloro-4-hydroxy-6-methyl-1*H*-pyridin-2-one (19.2 g, 0.12 mol) and DBU (19.9 mL, 0.13 mol) were dissolved in 70 mL of NMP. 2,4-Difluorobenzylbromide (17 mL, 0.13 mol) was added

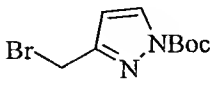
dropwise and the reaction was heated at 80 °C for 6 hours. The reaction was cooled to room temperature, the solid was filtered, and washed with NMP and hexanes. The solid was dried in a vacuum oven overnight to give a white solid (4.4 g, 13%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (br s, 1H), 7.63 (app q, J = 9 Hz, 1H), 7.33 (app t, J = 10 Hz, 1H), 7.16 (app t, J = 9 Hz, 1H), 6.37 (s, 1H), 5.24 (s, 2H), 2.20 (s, 3H).

Step 4. Preparation of 3-Methylpyrazole-1-carboxylic acid *tert*-butyl ester.



3-Methyl-1H-pyrazole (5.3 g, 65 mmol), DMAP (0.79 g, 6.5 mmol), and di-*tert*-butyl dicarbonate (2.8 g, 13 mmol) were at room temperature in 90 mL of CH_3CN for 1 hour.. The reaction was evaporated on a rotary evaporator, and the resulting solid dissolved in EtOAc, washed with 1 N HCl, water and brine, dried ($MgSO_4$), filtered, and evaporated on a rotary evaporator to give a light yellow oil (11.4 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 2.7 Hz, 1H), 6.17 (d, J = 2.7 Hz, 1H), 2.32 (s, 3H), 1.63 (s, 9H).

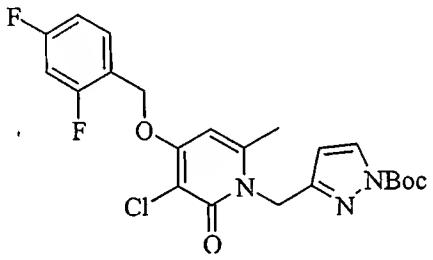
Step 5. Preparation of 3-Bromomethylpyrazole-1-carboxylic acid *tert*-butyl ester.



3-Methylpyrazole-1-carboxylic acid *tert*-butyl ester (6.0 g, 33 mmol), N-bromosuccinimide (1.0 g, 5.6 mmol) and benzoyl peroxide (50 mg) were dissolved in 20 mL of carbon

tetrachloride. The reaction was heated at reflux for 16 h. The reaction was cooled to room temperature, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:4 EtOAc/hexanes) gave a light yellow oil (4.5 g, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 2.6 Hz, 1H), 6.47 (d, J = 2.6 Hz, 1H), 4.48 (s, 2H), 1.64 (s, 9H).

Step 6. Preparation of 3-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2*H*-pyridin-1-ylmethyl]pyrazole-1-carboxylic acid *tert*-butyl ester.

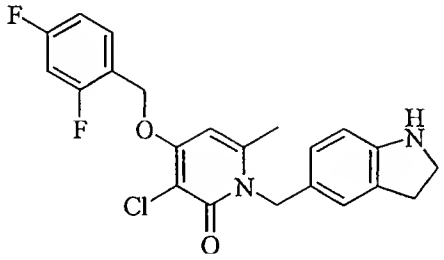


3-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2*H*-pyridin-1-ylmethyl]pyrazole-1-carboxylic acid *tert*-butyl ester was prepared by a procedure similar to the one described for Example 401 gave a yellow solid (1.4 g, 39%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 - 7.49 (m, 2H), 6.97 - 6.81 (m, 2H), 6.35 (d, J = 2.0 Hz, 1H), 6.01 (s, 1H), 5.32 (s, 2H), 5.26 (s, 2H), 2.52 (s, 3H), 1.62 (s, 9H).

Step 7. Preparation of the title compound Example 632 3-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2*H*-pyridin-1-ylmethyl]pyrazole-1-carboxylic acid *tert*-butyl ester (0.16 g, 0.34 mmol) was heated to 140 °C for 16 h. The reaction mixture was cooled to room temperature. Recrystallization from methylene chloride/hexanes provided an off-white solid (1.0 g, 91%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.67 (br s, 1H),

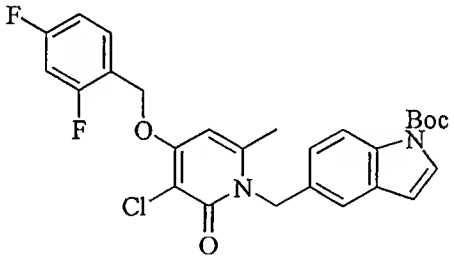
7.67 - 7.60 (m, 2H), 7.34 (dt, J = 10.5, 2.5 Hz, 1H), 7.17 (dt, J = 8.5, 1.6 Hz, 1H), 6.52 (s, 1H), 6.10 (d, J = 1.9 Hz, 1H), 5.27 (s, 2H), 5.20 (s, 2H), 2.48 (s, 2H).

Example 633



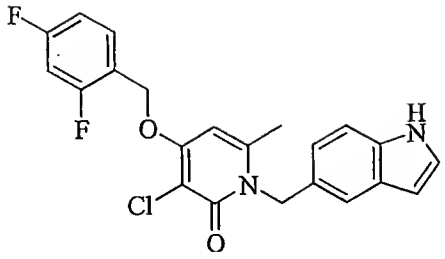
3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1-(2,3-dihydro-1H-indol-5-ylmethyl)-1H-pyridin-2-one

Step 1. Preparation of 5-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]indole-1-carbamic acid tert-butyl ester



5-[3-Chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]indole-1-carbamic acid tert-butyl ester was prepared by a procedure similar to the one described for Example 632 as an off-white solid (2.5 g, 61%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (d, J = 8.5 Hz, 1H), 7.70 - 7.62 (m, 2H), 7.39 - 7.32 (m, 2H), 7.21 - 7.13 (m, 2H), 6.70 (d, J = 3.8 Hz, 1H), 6.66 (s, 1H), 5.40 (s, 2H), 5.29 (s, 2H), 2.33 (s, 3H), 1.62 (s, 9H).

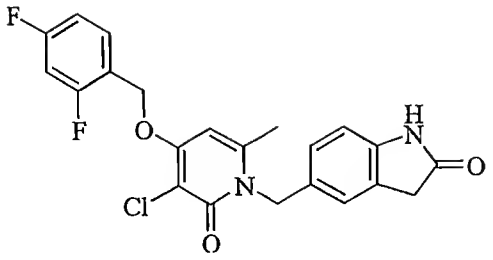
Step 2. Preparation of 3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1-(1H-indol-5-ylmethyl)-1H-pyridin-2-one .



5-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]indole-1-carbamic acid tert-butyl ester (1.08g, 2.1 mmol) dissolved in 40 mL of DMSO was stirred at 120 °C for 20 hours. The reaction was cooled to room temperature, diluted with water, and washed 5 times with ethyl acetate. The combined organics were washed 1 time with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. ^1H NMR (300 MHz, DMSO-d_6) δ 11.1 (br s, 1H), 7.67 (d, J = 6.7 Hz, 1H), 7.36 - 7.32 (m, 2H), 7.23 (s, 1H), 7.18 (d, J = 2.3 Hz, 1H), 6.93 (dd, J = 8.4, 1.2 Hz, 1H), 6.57 (s, 1H), 6.38 (s, 1H), 5.37 (s, 2H), 5.29 (s, 2H), 2.35 (s, 3H).

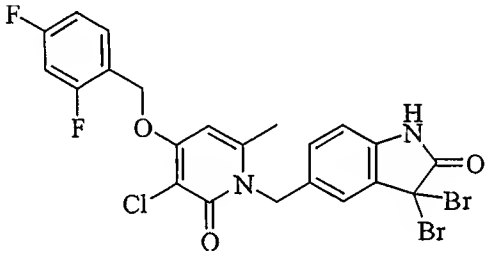
Step 3. 3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1-(1H-indol-5-ylmethyl)-1H-pyridin-2-one (, from Step 2) (1.7 g, 4.1 mmol) was stirred in 26 mL of acetic acid and $NaCNBH_3$ (0.27 g, 4.3 mmol) was added portionwise. The reaction was stirred for 1 hour. The reaction was diluted water, and washed 5 times with ethyl acetate. The combined organics were washed 1 time with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 100% EtOAc) gave a white solid (1.2 g, 71%): ^1H NMR (300 MHz, DMSO-d_6) δ 7.64 (app q, J = 8.5 Hz, 1H), 7.34 (dt, J = 9.5, 2.6 Hz, 1H), 7.17 (app t, J = 8.5, 1H), 6.82 (s, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.53 (s, 1H), 6.42 (d, J = 8.0 Hz, 1H), 5.48 (br s, 1H), 5.27 (s, 2H), 5.13 (s, 2H), 3.37 (t, J = 8.3 Hz, 2H), 2.82 (t, J = 8.3 Hz, 2H), 2.35 (s, 3H).

Example 634



5-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-1,3-dihydro-indol-2-one

Step 1. Preparation of 5-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-3,3-dibromo-1H-indol-2-one.

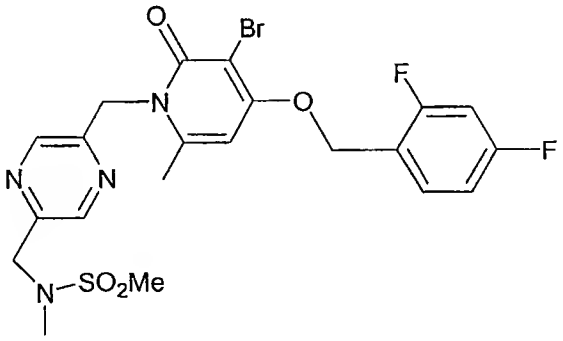


3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1-(1H-indol-5-ylmethyl)-1H-pyridin-2-one (0.45 mg, 1.1 mmol)(example 633, step 2) was suspended in 11 mL of tert-butanol and pyridinium bromide perbromide (1.04 g, 3.3 mmol) was added portionwise. The reaction was stirred for 16 hours. The reaction was diluted with water, and washed 4 times with ethyl acetate. The combined organics were washed 1 time with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Trituration with methylene chloride gave an off-white solid (0.25 g, 39%): ^1H NMR (300 MHz, DMSO-d_6) δ 11.26 (br s, 1H), 7.66 (app q, J = 8.6 Hz, 1H), 7.48 (s, 1H), 7.35 (dt, J = 10.5, 2.5 Hz, 1H), 7.18 (dt, J = 8.7, 1.9, 1H), 7.05 (dd, J =

8.2, 1.5, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.61 (s, 1H), 5.29 (s, 4H), 2.36 (s, 3H).

Step 2. 5-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-3,3-dibromo-1H-indol-2-one (0.2 g, 0.34 mmol) was suspended in 5 mL of acetic acid, and zinc metal (0.22 g, 3.4 mmol) was added. The reaction was stirred for 48 hours. The reaction was diluted with water, and washed 2 times with ethyl acetate. The combined organics were washed 1 time with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 100% EtOAc) gave a white solid (0.12 g, 82%): ^1H NMR (300 MHz, DMSO-d_6) δ 10.37 (br s, 1H), 7.65 (app q, J = 6.9 Hz, 1H), 7.34 (dt, J = 8.2, 2.5 Hz, 1H), 7.18 (dt, J = 7.1, 1.9, 1H), 6.98 (br s, 2H), 6.77 (d, J = 8.4 Hz, 1H), 6.57 (s, 1H), 5.28 (s, 2H), 5.23 (s, 2H), 3.44 (s, 2H), 2.34 (s, 3H).

Example 635

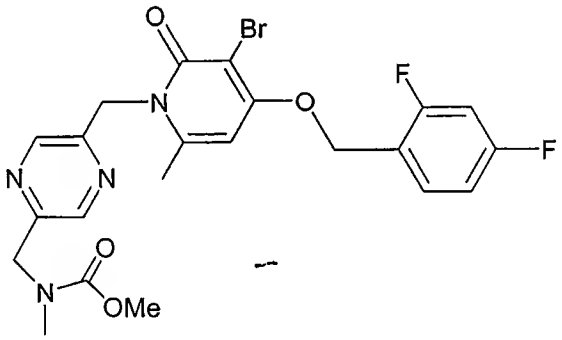


N-[(5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazin-2-yl)methyl]-N-methylmethanesulfonamide

To a suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one (0.16 g, 0.34 mmol) in acetonitrile at 0 °C was

added triethylamine (0.043 g, 0.42 mmol), followed by the addition of methane sulfonylchloride (0.047 g, 0.41 mmol) and stirred at room temperature for 1 h under argon atmosphere. The solvents were removed in vacuo and the residue was triturated with water and filtered. It was washed with water an, acetonitrile and dried in vacuo to afford 0.11 g of material. ^{1}H NMR (CD_3OD/ 400 MHz) δ 8.62 (s, 1H), 8.55 (s, 1H), 7.61 (m, 1H), 7.0 (m, 2H), 6.53 (s, 1H), 5.47 (s, 2H), 5.29 (s, 2H), 4.49 (s, 2H), 2.95 (s, 3H), 2.85 (s, 3H), and 2.55 (s, 3H); ^{19}F NMR(CD_3OD/ 400 MHz) -111.70(m) and -116.07 (m); ES-HRMS m/z 543.0515(M+H calcd for $C_{21}H_{22}BrF_2N_4O_4S$ requires 543.0508).

Example 636

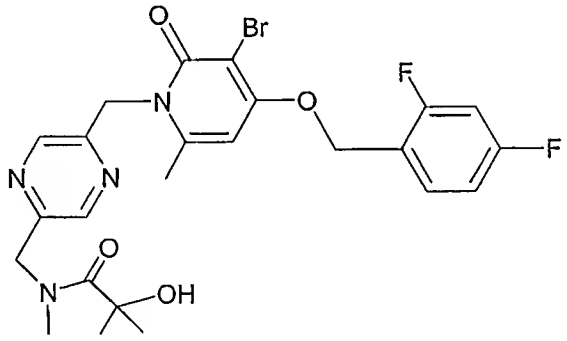


Methyl (5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazin-2-yl)methyl(methyl)carbamate

To a cold (5 °C) solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one (0.20 g, 0.4 mmol) in DMF (2.0 ml), was added methylchloroformate (0.049 g, 0.52 mmol), followed by the addition of triethylamine (0.072 g, 0.71 mmol). The mixture was stirred at 5 °C for 30 min and at room temperature for an additional 30 min and concentrated in vacuo . The residue was

partitioned between water (5.0 mL) and EtOAc (10.0 mL). The organic extract was washed with water, dried (Na_2SO_4), and concentrated to dryness. The resulting material was purified by reverse-phase HPLC using 10 -90 % CH_3CN/ Water gradient (60 min) at a flow rate of 70 mL/min. The appropriate fractions (m/z = 523 M+H) were combined and freeze dried to give a white powder. This was partitioned between 5% $NaHCO_3$ (10 mL) and EtOAc (15 mL). The organic layer was washed with water, dried (Na_2SO_4), and concentrated to dryness to afford the title compound (0.12 g, 53%) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 8.59 (s, 1H), 8.41(m, 1H), 7.60 (m, 1H), 7.05 (m, 2H), 6.52 (s, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 4.58 (s, 2H), 3.69 and 3.64 (s, 3H), 2.97 (s, 3H), 2.85 (s, 3H), and 2.55 (s, 3H); ^{19}F NMR(CD_3OD/ 400 MHz) -111.69(m) and -116.09 (m); ES-HRMS m/z 523.0775(M+H calcd for $C_{22}H_{22}BrF_2N_4O_4$ requires 523.0787).

Example 637

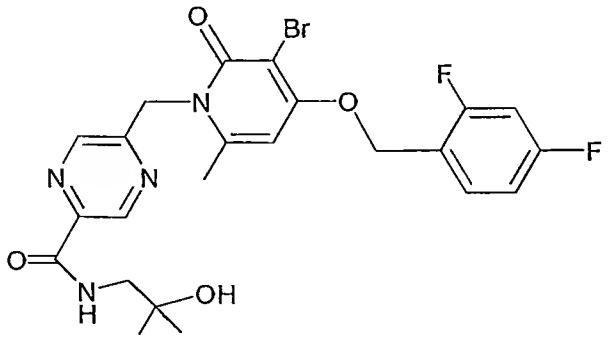


N-[(5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazin-2-yl)methyl]-2-hydroxy-N,2-dimethylpropanamide

To a cold (5 °C) solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one (0.24 g, 0.52 mmol) in DMF (2.0 ml), was added 2-

acetoxyisobutyryl chloride (0.093g, 0.56 mmol), followed by the addition of triethylamine (0.072 g, 0.71 mmol). The mixture was stirred at room temperature for an additional 2 h and concentrated in vacuo . The residue was partitioned between water (5.0 mL) and EtOAc (15.0 mL). The EtOAc extract was washed with water, dried (Na_2SO_4), and concentrated to dryness. The resulting material (0.2 g) was stirred with 1M. LiOH (0.5 mL, MeOH,/Water 1:1v/v) at room temperature for 3h, cooled, acidified with trifluoroacetic acid and the product was purified by reverse-phase HPLC using 10 -90 % CH_3CN/ Water gradient (60 min) at a flow rate of 70 mL/min. The appropriate fractions (m/z = 551 M+H) were combined and freeze dried to give a white powder. This was partitioned between 5% $NaHCO_3$ (10 mL) and EtoAc (15 mL). The organic layer was washed with water, dried (Na_2SO_4), and concentrated to dryness to afford the title compound (0.075 g) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 8.59 (s, 1H), 8.41(br, 1H), 7.60 (m, 2H), 7.01 (m, 2H), 6.52 (s, 1H), 5.45 (s, 2h), 5.29 (s, 2H),

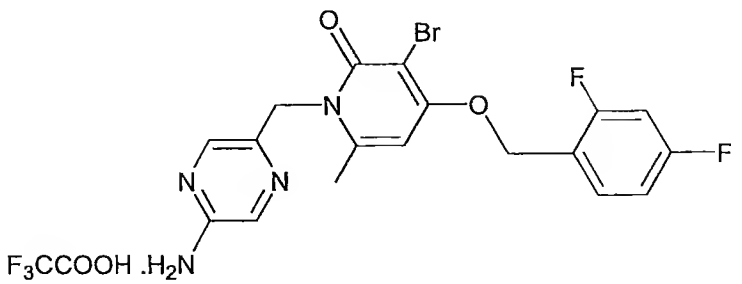
Example 638



5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)pyrazine-2-carboxamide

To a solution of 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid (0.42 g, 0.9 mmol) in DMF (3.0 mL) was added isobutylchloroformate (0.126 g, 0.13 mmol) followed by the addition of N-methylmorpholine (0.11 g, 1.1 mmol) and stirred at -10 °C, under argon atmosphere. After 20 min, added a solution of 1,1 dimethyl-2-aminoethanol hydrochloride (0.135g, 1.1 mmol) in DMF (2.0 mL) containing N-methylmorpholine (0.11 g, 1.1 mmol). The mixture was stirred at room temperature for 1 h, and concentrated to dryness in vacuo. The resulting residue was purified by reverse-phase HPLC using 10 -90 % CH_3CN/ Water gradient (60 min) at a flow rate of 70 mL/min. The appropriate fractions (m/z = 537 M+H) were combined and freeze dried to give a white powder. This was partitioned between 5% $NaHCO_3$ (10 mL) and EtOAc (15 mL). The organic layer was washed with water, dried (Na_2SO_4), and concentrated to dryness to afford the title compound (0.35 g, 75%) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 9.1 (d, 1H, J = 1.6 Hz), 8.71 (d, 1H, J = 1.6 Hz), 7.61 (m 1H), 7.02 (m, 2H), 6.54 (s, 1H), 5.54 (s, 2H), 5.30 (s, 2h). 3.30 (s, 2h), 2.55 (s, 3H), and 1.21 (s, 6H); ^{19}F NMR(CD_3OD/ 400 MHz) -111.67(m) and -116.05 (m); ES-HRMS m/z 537.0948 (M+H calcd for $C_{23}H_{24}BrF_2N_4O_4$ requires 537.0943).

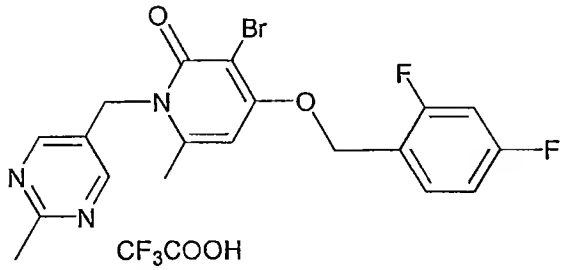
Example 639



1-[(5-Aminopyrazin-2-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate

A mixture of 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid (0.70g, 1.5 mmol) diphenylphosphoryl azide (0.51 g, 1.8 mmol) in dimethylacetamide (15.0 mL) and t-butanol (5.0 mL) containing triethylamine (0.18 g, 1.8 mmol) was heated at 90 °C for 6 h under argon atmosphere. The reaction mixture was cooled, filtered the precipitate. It was washed with acetonitrile and dried to obtain 0.22 g of the unreacted acid. The combilned filtrate and the washings were concentrated in vacuo and the resulting material was purified by reverse-phase HPLC using 10 -90 % CH_3CN/ Water gradient (60 min) at a flow rate of 70 mL/min. The appropriate fractions (m/z = 437 M+H) were combined and freeze dried to give the title compound (0.21g, 37%) as a white powder: ^1H NMR (DMSO-d_6/ 400 MHz) δ 7.88 (d, 1H, J = 1.2 Hz), 7.75 (d, 1H, J = 1.2 Hz), 7.61 (m 1H), 7.34 (m, 1H), 7.18 (m,1H), 6.49 (s, 1H), 5.25 (s, 2H), 5.10 (s, 2H), and 2.49 (s, 3H); ^{19}F NMR(CD_3OD/ 400 MHz) -111.72(m) and -116.11 (m); ES-HRMS m/z 437.0402(M+H calcd for $C_{18}H_{16}BrF_2N_4O_2$ requires 437.0419).

Example 640



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(3-methyl-1,2,4-triazin-6-yl)methyl]pyridin-2(1H)-one trifluoroacetate

Step 1: Preparation of (2-methylpyrimidin-5-yl)methanol trifluoroacetate

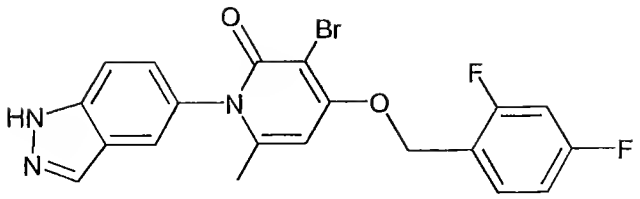
To solution of methyl 2-methylpyrimidinecarboxylate (2.6 g, 17.1 mmol) in THF was added dropwise diisobutylaluminumhydride (39.5 mL, 1M solution in THF) and stirred at -20 °C under argon atmosphere for 1.5 h, and at room temperature for 2 h. The reaction was quenched by the addition of powdered sodiumsulphate decahydrate (25 g), added THF (25 mL) and stirred at room temperature for 1h. This mixture was allowed to stand in the refrigerator overnight and filtered through a celite pad. The precipitate was thoroughly with warm THF (100 mL) containing 10% ethanol. The combined washings and the filtrate were concentrated to afford ayellow syrup, which was purified by reverse-phase HPLC using 10 -90 % CH_3CN/ Water gradient (60 min) at a flow rate of 70 mL/min. The appropriate fractions (m/z = 125 M+H) were combined and lyophilized to give the title compound (0.67 g, 32%) as its trifluoroacetate salt: ^1H NMR (CD_3OD/ 400 MHz) δ 8.65 (s, 2H) 4.62 (s, 2H), and 2.66 (s, 3H); ES-HRMS m/z 125.0678 (M+H calcd for $C_6H_9N_2O$ requires 125.0709).

Step 2: Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(3-methyl-1,2,4-triazin-6-yl)methyl]pyridin-2(1H)-one trifluoroacetate

To a solution of (2-methylpyrimidin-5-yl)methanol trifluoroacetate (0.9 g, 3.76 mmol) in dichloromethane (10 mL) at 0 °C, was added triethylamine (0.95 g, 9.41 mmol), followed by the addition of methanesulfonyl chloride (0.59 g, 5.17 mmol) and stirred at 0 °C for 1 h. After stirring for 1 h at room temperature, additional triethylamine (0.22 g) and methanesulfonyl chloride (0.15 g)were added and the mixture was stirred at room temperature for another hour under argon atmosphere. The reaction was quenched by the addition of cold water (15 mL) and stirred for 15 min. The organic layer was washed with water, followed by 5% sod. bicarbonate (2 x 15 mL), water, and dried (Na_2SO_4). After the removal of the solvent under reduced pressure, the residue was dried in a desiccator under vacuum for 4 h. This material was suspended in THF (10 mL) and DMF (5.0 mL), added 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1H)-one (0.5 g, 1.52 mmol) and NaH (0.04 g). The resulting mixture was heated at 65 °C for 16 h under argon atmosphere. The solvents were distilled under vacuum and the residue was purified by reverse-phase HPLC using 10 -90 % CH_3CN/ Water gradient (60 min) at a flow rate of 70 mL/min. The appropriate fractions (m/z = 436 M+H) were combined and freeze dried to give the title compound (0.045 g,) as its trifluoroacetate salt: ^1H NMR (CD_3OD/ 400 MHz) δ 8.58 (s, 2H) 7.61 (m, 1H), 7.01 (m, 2H), 6.53 (s, 1H), 5.37 (s, 2h), 5.29 (s, 2H), 2.65 (s, 3H), and 2.46 (s, 3H); ^{19}F NMR(CD_3OD/ 400 MHz)

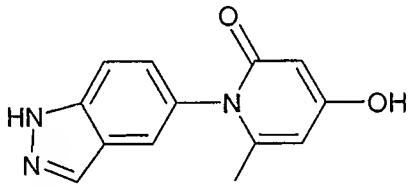
-111.62 (m), and -116.08 (m); ES-HRMS m/z 436.0433(M+H calcd for $C_{19}H_{17}BrF_2N_3O_2$ requires 436.0467).

Example 641



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(1H-indazol-5-yl)-6-methylpyridin-2(1H)-one

Step 1: Preparation of 4-hydroxy-1-(1H-indazol-5-yl)-6-methylpyridin-2(1H)-one



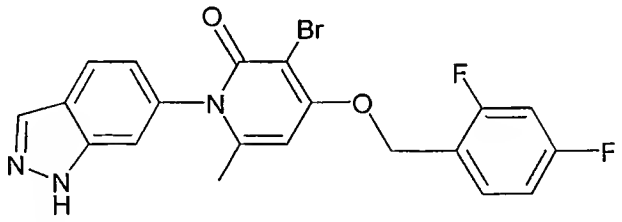
A mixture of 4- hydoxy-6-methyl-2-pyrone (3.75 g, 0.029 mol) and 5-aminoindazole (4.0 g, 0.03 mol) in water (70 ml) was heated at 90 °C under argon for 1 h. The mixture was cooled, decanted the supernatant and residue was triturated with ethanol, cooled and filtered the solid. It was washed with cold ethanol, and dried. ^{1}H NMR (CD_3OD/ 400 MHz) δ 8.11 (s, 1H), 7.64 (m, 2H), 7.18 (d, 1H, J = 2.0 Hz), 7.16 (d, 1H, J = 2.0 Hz) 6.07 (m, 1H), 5.81 (d, 1H, J = 2.8 Hz), and 1.94 (s, 3H); ES-HRMS m/z 242.0962(M+H calcd for $C_{13}H_{12}N_3O_2$ requires 242.0924).

Step 2:

A mixture of 4-hydroxy-1-(1H-indazol-5-yl)-6-methylpyridin-2(1H)-one (0.2g, 0.83 mmol), N- bromosuccinmide (0.15 g, 0.84 mmol) in dichloromethane (4.0 mL) and acetic acid (1.0 mL) was stirred at room temperature under argon atmosphere for 2.5 h. After the removal of the solvents, the

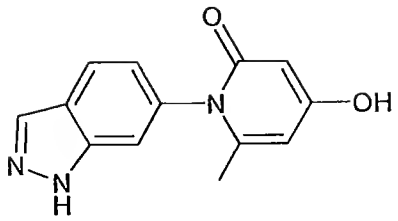
residue was dried in vacuo for 4 h in a desiccator. It was then suspended in DMF (3.0 mL), potassium carbonate (0.1g), and 2,4 difluorobenzyl bromide were added and mixture was stirred at room temperature for 3 h. DMF was distilled in vacuo and the residue was purified by reverse-phase HPLC using 10 -90 % CH_3CN/ Water gradient (60 min) at a flow rate of 70 mL/min. The appropriate fractions (m/z = 537 M+H) were combined and freeze dried to give a white powder. This was partitioned between 5% $NaHCO_3$ (10 mL) and EtOAc (15 mL). The organic layer was washed with water, dried (Na_2SO_4), and concentrated to dryness to afford the title compound (0.075 g) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 8.13 (s, 1H), 7.68 (m, 3H), 7.20 (2d, 1H, J = 1.2 Hz), 7.05 (m, 2H), 6.61 (s, 1H), 5.35 (s, 2H), and 2.05 (s, 3H); ^{19}F NMR(CD_3OD/ 400 MHz) -111.62 (m) and -116.02 (m); ES-HRMS m/z 446.0305(M+H calcd for $C_{20}H_{15}BrF_2N_3O_2$ requires 446.0310).

Example 642



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(1H-indazol-6-yl)-6-methylpyridin-2(1H)-one

Step 1: Preparation of 4-hydroxy-1-(1H-indazol-6-yl)-6-methylpyridin-2(1H)-one

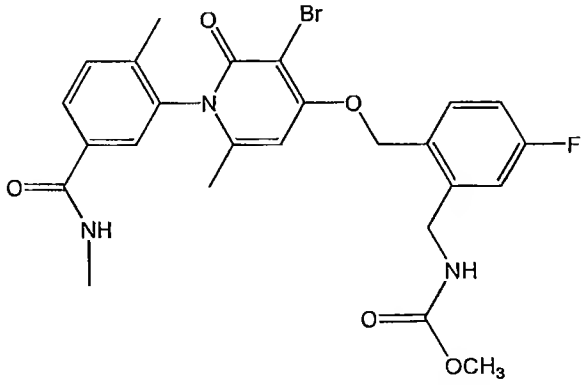


The title compound was prepared by a similar procedure described for 4-hydroxy-1-(1H-indazol-5-yl)-6-methylpyridin-2(1H)-one. Yield = 12%; ^{1}H NMR (CD_3OD/ 400 MHz) δ 8.12 (s, 1H), 7.90 (d, 1H, J = 8.0 Hz), 7.42 (s, 1H), 6.94 (d, 1H, J = 8.8 Hz) 6.08 (br s, 1H), 5.81 (d, 1H, J = 2.4 Hz), and 1.96 (s, 3H); ES-HRMS m/z 242.0946(M+H calcd for $C_{13}H_{12}N_3O_2$ requires 242.0924).

Step 2:

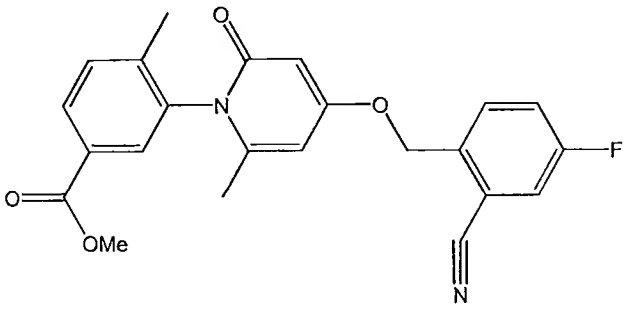
The title was prepared by a similar procedure described for 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(1H-indazol-5-yl)-6-methylpyridin-2(1H)-one. ^{1}H NMR (CD_3OD/ 400 MHz) δ 8.14 (s, 1H), 7.93 (d, 1H, J = 8.4Hz), 7.61 (m 1H), 7.46 (s, 1H), 7,04 (m, 2H), 6.98 (m, 1H) 6.62 (s, 1H), 5.36 (s, 2H), and 2.06 (s, 3H); ^{19}F NMR(CD_3OD/ 400 MHz) -111.62 (m) and -116.03 (m); ES-HRMS m/z 446.0302(M+H calcd for $C_{13}H_{12}N_3O_2$ requires 446.0310).

Example 643



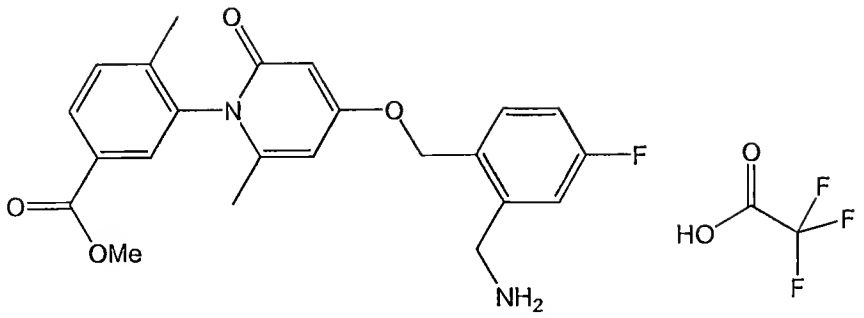
methyl 2-{[(3-bromo-6-methyl-1-{2-methyl-5-[(methylamino)carbonyl]phenyl}-2-oxo-1,2-dihydropyridin-4-yl)oxy]methyl}-5-fluorobenzylcarbamate

Step 1: Preparation of methyl 3-[4-[(2-cyano-4-fluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate .



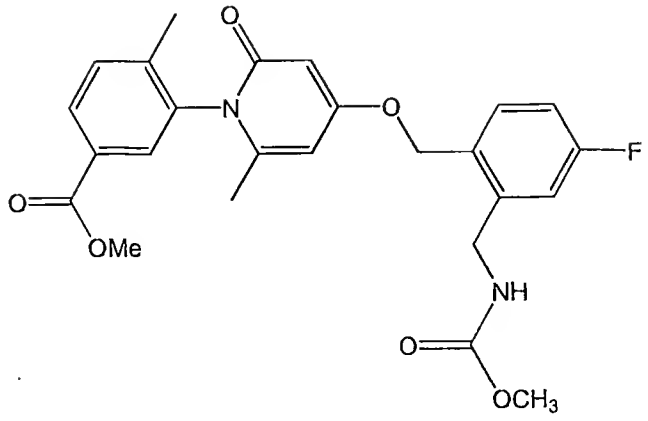
To a cooled (0°C) solution of 2-(bromomethyl)-5-fluorobenzonitrile (4.31 g, 20.1 mmol) and methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-methylbenzoate (5.00 g, 18.3 mmol) in DMF (20 mL) was added K_2CO_3 (3.00 g, 22.0 mmol). The reaction was allowed to warm to RT and stirred overnight. Additional 2-(bromomethyl)-5-fluorobenzonitrile (0.39 g, 1.83 mmol) and K_2CO_3 (0.25 g, 1.83 mmol) were added and the reaction heated at 60°C for 2h. Solvent removed by distillation. Reaction neutralized with 5% citric acid (50 mL). Organic products were extracted in DCM (3 x 25 mL), dried over Na_2SO_4, filtered, and concentrated to a thick dark brown oil. Purified by silica gel flash column chromatography using EtOAc as the eluent to give the product as a brown solid, dried in vacuo (6.18 g, 76%). ^1H NMR (CD_3OD/ 400MHz) δ8.03 (m, 1H), 7.76 (m, 2H), 7.66 (m, 1H), 7.52 (m, 2H), 6.24 (s, 1H), 6.09 (s, 1H), 5.27 (s, 2H), 3.89 (s, 3H), 2.12 (s, 3H), 1.90 (s, 3H). ESHRMS m/z 407.1408 (M+H calculated for $C_{23}H_{20}FN_2O_4$ requires 407.1402).

Step 2: Preparation of methyl 3-[4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate trifluoroacetate



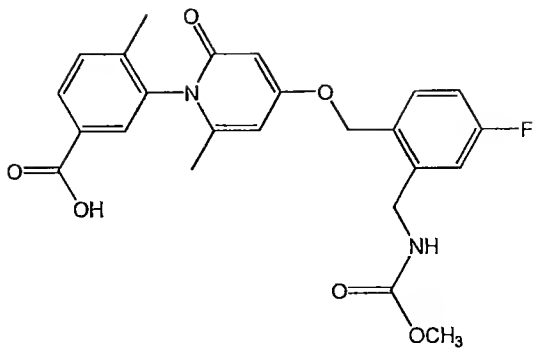
To a cooled (0°C) solution of methyl 3-[4-[(2-cyano-4-fluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (from Step 1) (0.510 g, 1.25 mmol) in THF (5 mL) was added dropwise BH_3THF (2.51 mL, 2.51 mmol). The reaction was then stirred at RT for 2.5h. Reaction cooled (0°C), quenched by the slow addition of MeOH, concentrated, and purified by preparatory HPLC. The product was isolated by freeze-drying and evaporation of the solvent to give a white solid, dried in vacuo (0.39 g, 76%). ^1H NMR (CD_3OD/ 400MHz) δ8.04 (m, 1H), 7.75 (s, 1H), 7.63 (m, 1H), 7.55 (d, 1H, J = 8.4 Hz), 7.32 (m, 1H), 7.24 (m, 1H), 6.25 (s, 1H), 6.12 (s, 1H), 5.23 (s, 2H), 4.25 (s, 2H), 3.90 (s, 3H), 2.11 (s, 3H), 1.90 (s, 3H). ESHRMS m/z 411.1691 (M+H calculated for $C_{23}H_{24}FN_2O_4$ requires 411.1715).

Step 3: Preparation of methyl 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate .



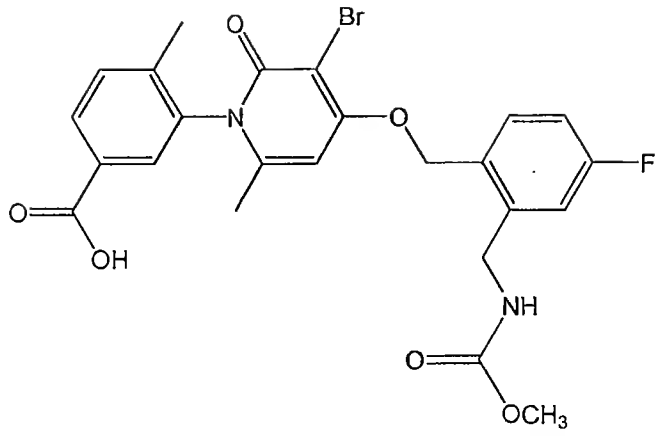
To a cooled (0°C) solution of methyl 3-[4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate trifluoroacetate (from Step 2) (0.50 g, 0.95 mmol) in DMA (4 mL) was added 4-methylmorpholine (0.21 mL, 1.9 mmol) and methyl chloroformate (0.08 mL, 1.0 mmol). Reaction was stirred at RT for 1h. Solvent removed by distillation. Crude product purified by preparatory HPLC. Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (30 mL) and extracted in DCM (3 x 25 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated to a white solid, dried in vacuo (0.36 g, 81%). ^1H NMR (CD_3OD/400MHz) δ8.03 (m, 1H), 7.77 (s, 1H), 7.53 (d, 1H, J = 7.6 Hz), 7.47 (m, 1H), 7.12 (m, 1H), 7.03 (m, 1H), 6.21 (s, 1H), 6.08 (s, 1H), 5.18 (s, 2H), 4.38 (s, 2H), 3.89 (s, 3H), 3.65 (s, 3H), 2.12 (s, 3H), 1.89 (s, 3H). ESHRMS m/z 469.1767 (M+H calculated for $C_{25}H_{26}FN_2O_6$ requires 469.1769).

Step 4: Preparation of 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid .



To methyl 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (from Step 3) (0.17 g, 0.36 mmol) was added 1.5 N NaOH solution in 1:1 MeOH:water (0.39 mL, 0.59 mmol). The reaction mixture was stirred at 60°C for 2.5h. The solution was cooled (0°C), neutralized by the slow addition of 5% citric acid, and organic products extracted in DCM. A white solid suspended in the organic layer was filtered, washed with DCM and water, dried in vacuo, and found to be the desired product (0.090 g, 55%). ^{1}H NMR (CD_3OD/ 400MHz) δ8.03 (m, 1H), 7.75 (s, 1H), 7.52 (d, 1H, J = 8.0 Hz), 7.47 (m, 1H), 7.12 (m, 1H), 7.03 (m, 1H), 6.21 (s, 1H), 6.08 (s, 1H), 5.18 (s, 2H), 4.38 (s, 2H), 3.65 (s, 3H), 2.12 (s, 3H), 1.90 (s, 3H). ESHRMS m/z 455.1632 (M+H calculated for $C_{24}H_{24}FN_2O_6$ requires 455.1613).

Step 5: Preparation of 3-[3-bromo-4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid.



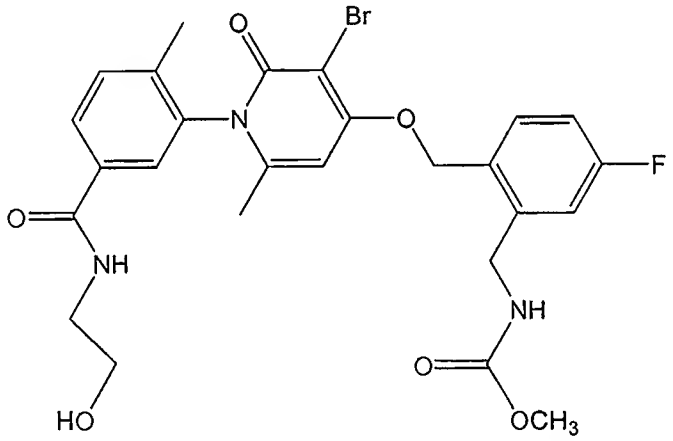
NBS (0.69 g, 3.85 mmol) was added to a solution of 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (from Step 4) (1.75 g, 3.85 mmol) in DCM (45 mL). After 1.5h, solvent removed on rotary evaporator. Solid dissolved in EtOAc and hexane added, resulting in a solid precipitate. Solid filtered. Solid subsequently dissolved in DCM and washed with water. Organic layer dried over Na_2SO_4, filtered, and concentrated. Pale yellow solid dried in vacuo (1.47 g, 72%). ^1H NMR (CD_3OD/ 400MHz) δ8.04 (m, 1H), 7.77 (s, 1H), 7.54 (m, 2H), 7.13 (m, 1H), 7.05 (m, 1H), 6.68 (s, 1H), 5.40 (s, 2H), 4.44 (s, 2H), 3.64 (s, 3H), 2.09 (s, 3H), 1.99 (s, 3H). ESHRMS m/z 533.0700 and 535.0677 (M+H calculated for $C_{24}H_{23}BrFN_2O_6$ requires 533.0718 and 535.0701).

Step 6: Preparation of the title compound .

To a cooled (-10°C) solution of 3-[3-bromo-4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (0.07 g, 0.13 mmol) in DMF (2.0 mL) was added isobutyl chloroformate (0.02 mL, 0.16 mmol) and 4-methylmorpholine (0.02 mL, 0.16 mmol). After 15min, 2.0M methylamine in THF (0.01 mL, 0.20 mmol) was added. Solvent removed by distillation after 30min. Crude product purified by preparatory HPLC. Acetonitrile was evaporated and

the solution washed with 5% $NaHCO_3$ (30 mL) and extracted in DCM (3 x 25 mL). The organic extracts were dried over Na_2SO_4, filtered, concentrated, and dried in vacuo to give a white foam, (0.061 g, 86%). ^1H NMR (CD_3OD/ 400MHz) δ7.85 (m, 1H), 7.54 (m, 3H), 7.14 (m, 1H), 7.05 (m, 1H), 6.68 (s, 1H), 5.40 (s, 2H), 4.43 (s, 2H), 3.64 (s, 3H), 2.89 (s, 3H), 2.08 (s, 3H), 1.99 (s, 3H). ESHRMS m/z 546.0987 and 548.1018 (M+H calculated for $C_{25}H_{26}BrFN_3O_5$ requires 546.1034 and 548.1018).

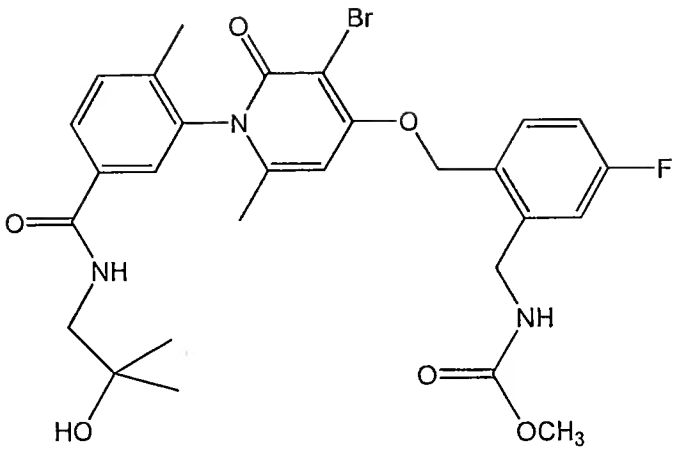
Example 644



methyl 2-({[3-bromo-1-(5-{[(2-hydroxyethyl)amino]carbonyl}-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

The title compound was prepared using a procedure similar to that used in the preparation of Example 643. ^1H NMR (CD_3OD/ 400MHz) δ7.88 (m, 1H), 7.61 (s, 1H), 7.53 (m, 2H), 7.13 (m, 1H), 7.04 (m, 1H), 6.68 (s, 1H), 5.41 (s, 2H), 4.43 (s, 2H), 3.68 (t, 2H, J = 5.6 Hz), 3.64 (s, 3H), 3.48 (t, 2H, J = 5.6Hz), 2.08 (s, 3H), 2.00 (s, 3H). ESHRMS m/z 576.1101 and 578.1072 (M+H calculated for $C_{26}H_{28}BrFN_3O_6$ requires 576.1140 and 578.1124).

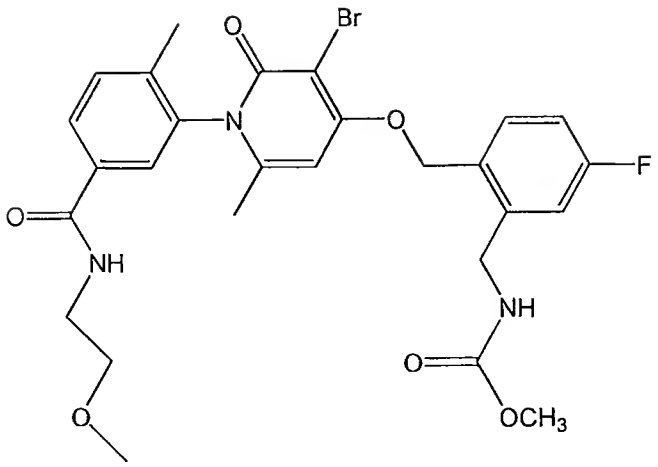
Example 645



methyl 2-({[3-bromo-1-(5-{[(2-hydroxy-2-methylpropyl)amino]carbonyl}-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

The title compound was prepared using a procedure similar to that used in the preparation of Example 643. ^{1}H NMR (CD_3OD/400MHz) δ7.89 (m, 1H), 7.63 (s, 1H), 7.54 (m, 2H), 7.13 (m, 1H), 7.04 (m, 1H), 6.69 (s, 1H), 5.41 (s, 2H), 4.43 (s, 2H), 3.64 (s, 3H), 3.38 (s, 2H), 2.09 (s, 3H), 2.01 (d, 6H, J = 3.2 Hz), 1.21 (s, 3H). ESHRMS m/z 604.1412 and 606.1418 (M+H calculated for $C_{28}H_{32}BrFN_3O_6$ requires 604.1453 and 606.1438).

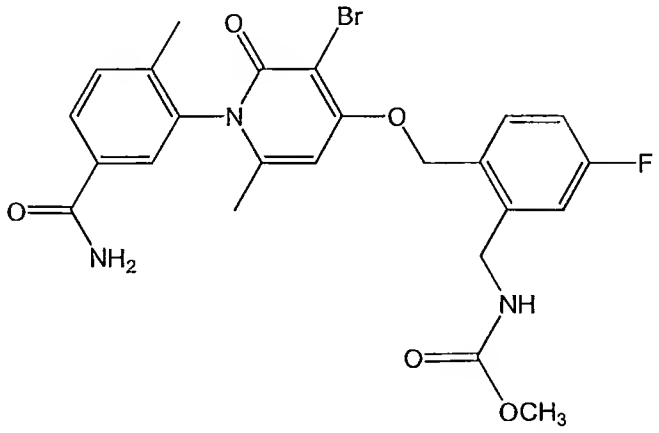
Example 646



methyl 2-({[3-bromo-1-(5-{[(2-methoxyethyl)amino]carbonyl}-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

The title compound was prepared using a procedure similar to that used in the preparation of Example 643. ^{1}H NMR (CD_3OD/400MHz) δ7.87 (m, 1H), 7.59 (s, 1H), 7.53 (m, 2H), 7.14 (m, 1H), 7.05 (m, 1H), 6.68 (s, 1H), 5.41 (s, 2H), 4.44 (s, 2H), 3.64 (s, 3H), 3.54 (s, 4H), 3.35 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H). ESHRMS m/z 590.1267 and 592.1219 (M+H calculated for $C_{27}H_{30}BrFN_3O_6$ requires 590.1297 and 592.1281).

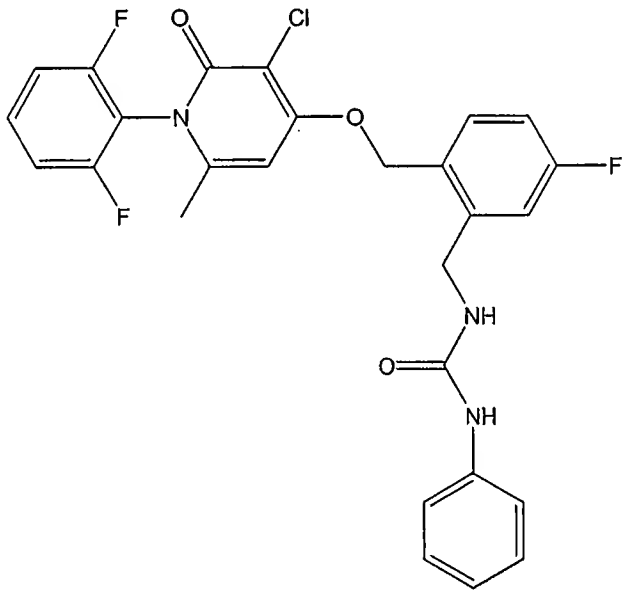
Example 647



methyl 2-[({1-[5-(aminocarbonyl)-2-methylphenyl]-3-bromo-6-methyl-2-oxo-1,2-dihydropyridin-4-yl}oxy)methyl]-5-fluorobenzylcarbamate

The title compound was prepared using a procedure similar to that used in the preparation of Example 643. ^{1}H NMR (CD_3OD/400MHz) δ7.91 (m, 1H), 7.64 (s, 1H), 7.54 (m, 2H), 7.14 (m, 1H), 7.05 (m, 1H), 6.68 (s, 1H), 5.40 (s, 2H), 4.44 (s, 2H), 3.64 (s, 3H), 2.09 (s, 3H), 2.00 (s, 3H). ESHRMS m/z 532.0836 and 534.0787 (M+H calculated for $C_{24}H_{24}BrFN_3O_5$ requires 532.0878 and 534.0861).

Example 648

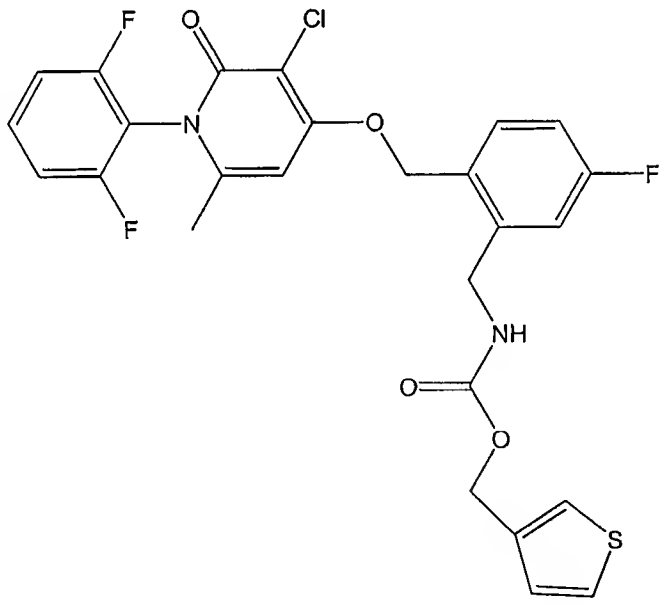


N-[2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzyl]-N'-phenylurea

To a cooled (0°C) solution of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-chloro-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0.25 g, 0.48 mmol)

in DMA (2.0 mL) was added 4-methylmorpholine (0.06 mL, 0.53 mmol) and phenyl isocyanate (0.06 mL, 0.53 mmol). The reaction was stirred at RT for 1.5h. Solvent distilled and crude product purified by preparatory HPLC. Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (30 mL) and extracted in DCM (3 x 25 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated to a white solid, dried in vacuo (0.18 g, 71%). ^1H NMR (CD_3OD/ 400MHz) δ7.60 (m, 1H), 7.54 (m, 1H), 7.33 (d, 2H, J = 7.6 Hz), 7.22 (m, 5H), 7.06 (m, 1H), 6.95 (t, 1H, J = 7.2 Hz), 6.73 (s, 1H), 5.44 (s, 2H), 4.53 (s, 2H), 2.07 (s, 3H). ESHRMS m/z 528.1304 (M+H calculated for $C_{27}H_{22}ClF_3N_3O_3$ requires 528.1296).

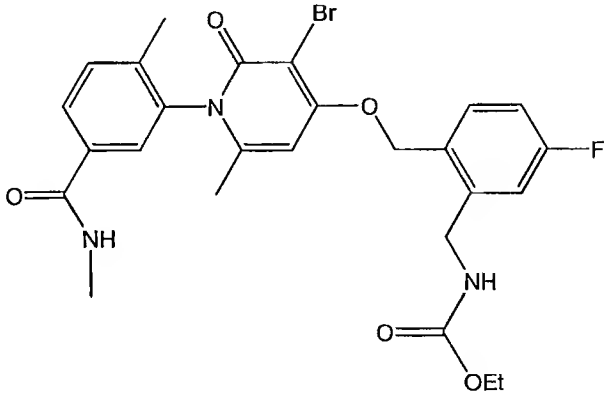
Example 649



thien-3-ylmethyl 2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

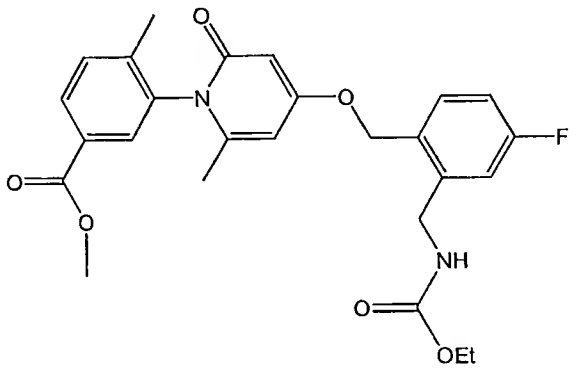
To a cooled (0°C) solution of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-chloro-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0.26 g, 0.50 mmol) and 1, 1-carbonyldiimidazole (0.10 g, 0.60 mmol) in DMA (2.0 mL) was added 4-methylmorpholine (0.06 mL, 0.55 mmol). After 1h at RT, 3-thiophenemethanol (0.09 mL, 0.99 mmol) was added. No product was observed after 2h at RT. NaH (0.01 g, 0.50 mmol) was added and the reaction stirred at 60°C. Reaction was complete after 20min. The reaction mixture was cooled (0°C) and acetic acid added to quench the reaction. Solvent removed by distillation. Crude product purified by preparatory HPLC. Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (30 mL) and extracted in DCM (3 x 25 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated to a white foam, dried in vacuo (0.20 g, 73%). ^1H NMR (CD_3OD/400MHz) δ7.61 (m, 1H), 7.52 (m, 1H), 7.34 (s, 2H), 7.23 (t, 3H, J = 8.4 Hz), 7.10 (m, 2H), 6.71 (s, 1H), 5.40 (s, 2H), 5.07 (s, 2H), 4.43 (s, 2H), 2.10 (s, 3H). ESHRMS m/z 549.0858 (M+H calculated for $C_{26}H_{21}ClF_3N_2O_4S$ requires 549.0857).

Example 650



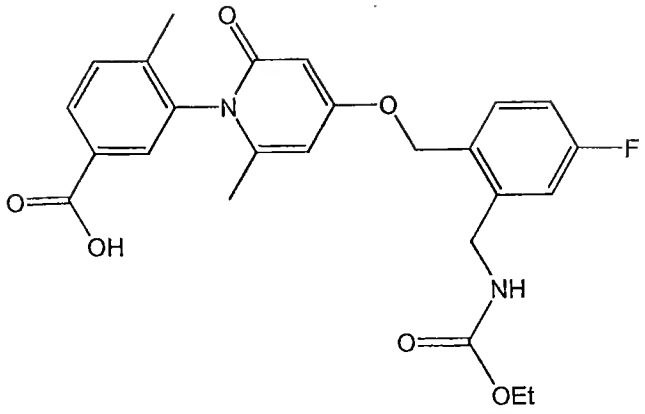
ethyl 2-{[(3-bromo-6-methyl-1-{2-methyl-5-[(methylamino)carbonyl]phenyl}-2-oxo-1,2-dihydropyridin-4-yl)oxy]methyl}-5-fluorobenzylcarbamate

Step 1: Preparation of methyl 3-[4-[(2-{[(ethoxycarbonyl)amino]methyl}-4-fluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate.



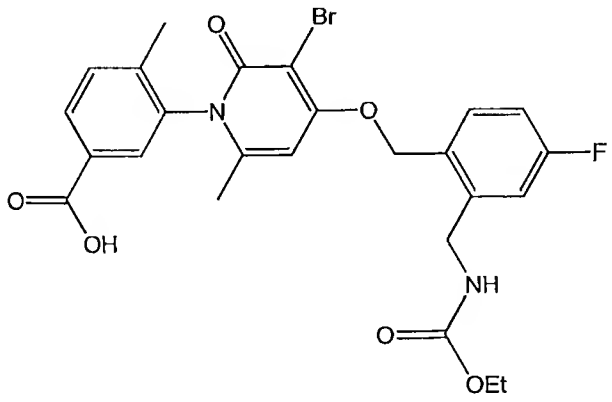
Prepared using a procedure similar to that used in the preparation of methyl 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate. ^{1}H NMR (CD_3OD/ 400MHz) δ8.03 (m, 1H), 7.76 (s, 1H), 7.53 (d, 1H, J = 8.0 Hz), 7.47 (m, 1H), 7.12 (m, 1H), 7.03 (m, 1H), 6.21 (s, 1H), 6.08 (s, 1H), 5.18 (s, 2H), 4.38 (s, 2H), 4.08 (q, 2H, J = 6.8 Hz), 3.89 (s, 3H), 2.12 (s, 3H), 1.89 (s, 3H), 1.23 (t, 3H, J = 6.8 Hz). ESHRMS m/z 483.1900 (M+H calculated for $C_{26}H_{28}FN_2O_6$ requires 483.1926).

Step 2: Preparation of 3-[4-[(2-{[(ethoxycarbonyl)amino]methyl}-4-fluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid .



Prepared using a procedure similar to that used in the preparation of 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid. ^{1}H NMR (CD_3OD/ 400MHz) δ8.03 (m, 1H), 7.74 (s, 1H), 7.48 (m, 2H), 7.11 (m, 1H), 7.03 (m, 1H), 6.21 (s, 1H), 6.08 (s, 1H), 5.18 (s, 2H), 4.38 (s, 2H), 4.08 (q, 2H, J = 7.2 Hz), 2.11 (s, 3H), 1.90 (s, 3H), 1.23 (t, 3H, J = 7.2 Hz). ESHRMS m/z 469.1738 (M+H calculated for $C_{25}H_{26}FN_2O_6$ requires 469.1769).

Step 3: Preparation of 3-[3-bromo-4-[(2-{[(ethoxycarbonyl)amino]methyl}-4-fluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid.



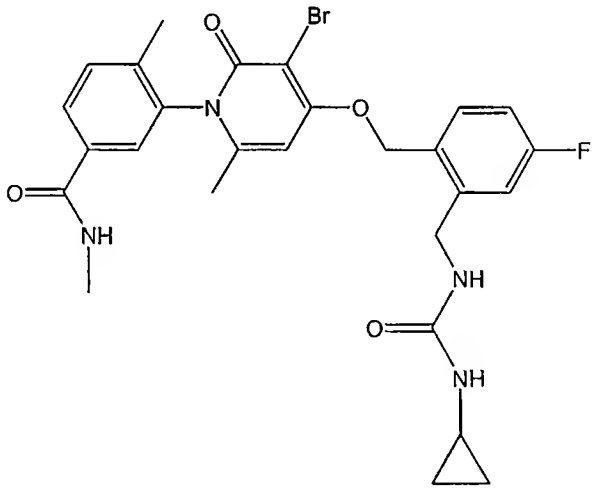
Prepared using a procedure similar to that used in Step 5 of the synthesis of Example 643. ^{1}H NMR (CD_3OD/ 400MHz) δ8.04

(m, 1H), 7.76 (s, 1H), 7.55 (m, 2H), 7.13 (m, 1H), 7.05 (m, 1H), 6.68 (s, 1H), 5.40 (s, 2H), 4.43 (s, 2H), 4.07 (m, 2H), 2.09 (s, 3H), 1.99 (s, 3H), 1.22 (t, 3H, J = 7.2 Hz). ESHRMS m/z 547.0842 and 549.0818 (M+H calculated for $C_{25}H_{25}BrFN_2O_6$ requires 547.0875 and 549.0858).

Step 4:

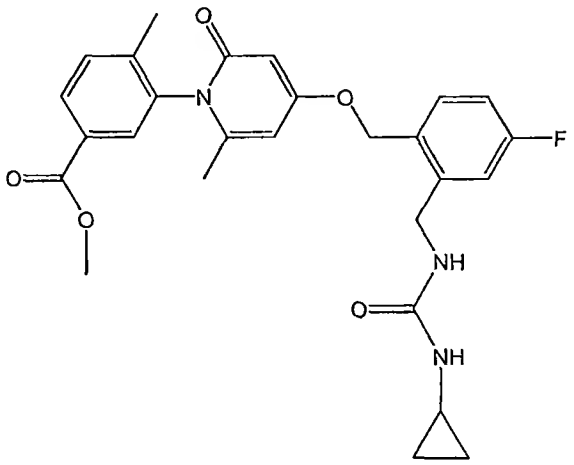
Prepared using a procedure similar to that used in the preparation of Example 643. ^{1}H NMR (CD_3OD/ 400MHz) δ7.85 (m, 1H), 7.54 (m, 3H), 7.13 (m, 1H), 7.04 (m, 1H), 6.68 (s, 1H), 5.40 (s, 2H), 4.43 (s, 2H), 4.07 (q, 2H), 2.89 (s, 3H), 2.08 (s, 3H), 1.99 (s, 3H), 1.23 (t, 3H, J = 7.2 Hz). ESHRMS m/z 560.1215 and 562.1193 (M+H calculated for $C_{26}H_{28}BrFN_3O_5$ requires 560.1191 and 562.1175).

Example 651



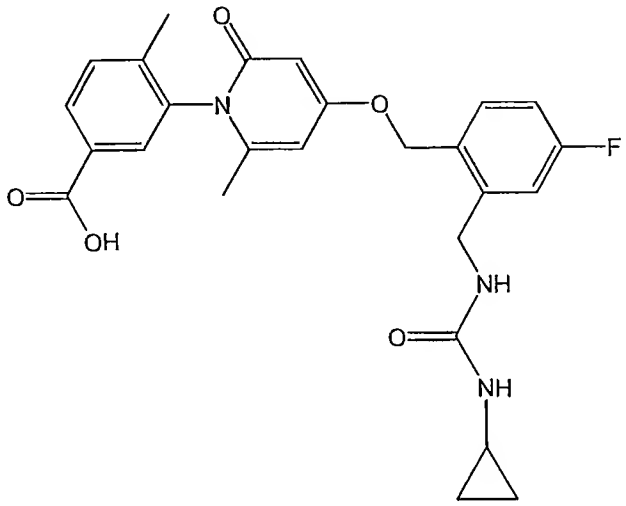
3-[3-bromo-4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide

Step 1: Preparation of methyl 3-[4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate .



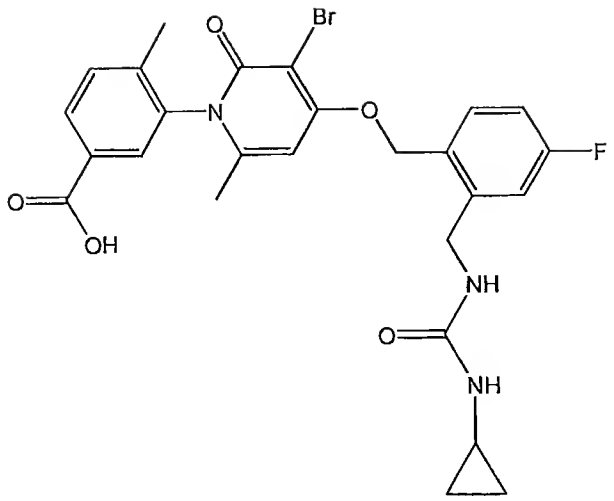
To a cooled (0°C) solution of methyl 3-[4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate trifluoroacetate () (1.13 g, 2.16 mmol) and 1,1-carbonyldiimidazole (0.42 g, 2.59 mmol) in DMA (8.0 mL) was added 4-methylmorpholine (0.36 mL, 3.2 mmol). Reaction was stirred at RT for 2h. DMA removed by distillation. Crude product purified by preparatory HPLC. Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (30 mL) and extracted in DCM (3 x 25 mL). The organic extracts were dried over Na_2SO_4, filtered, concentrated, and dried in vacuo (0.78 g, 73%). ^1H NMR (CD_3OD/ 400MHz) δ8.03 (m, 1H), 7.76 (s, 1H), 7.53 (d, 1H, J = 8.0 Hz), 7.46 (m, 1H), 7.12 (m, 1H), 7.01 (m, 1H), 6.22 (s, 1H), 6.08 (s, 1H), 5.19 (s, 2H), 4.44 (s, 2H), 3.89 (s, 3H), 2.48 (m, 1H), 2.12 (s, 3H), 1.89 (s, 3H), 0.70 (m, 2H), 0.47 (m, 2H). ESHRMS m/z 494.2076 (M+H calculated for $C_{27}H_{29}FN_3O_5$ requires 494.2086).

Step 2: Preparation of 3-[4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid .



Prepared using a procedure similar to that used in the preparation of 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid. ^{1}H NMR (CD_3OD/400MHz) δ8.02 (m, 1H), 7.74 (s, 1H), 7.48 (m, 2H), 7.12 (m, 1H), 7.01 (m, 1H), 6.22 (s, 1H), 6.08 (s, 1H), 5.19 (s, 2H), 4.44 (s, 2H), 2.48 (m, 1H), 2.11 (s, 3H), 1.90 (s, 3H), 0.69 (m, 2H), 0.47 (m, 2H). ESHRMS m/z 480.1921 (M+H calculated for $C_{26}H_{27}FN_3O_5$ requires 480.1929).

Step 3: Preparation of 3-[3-bromo-4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid

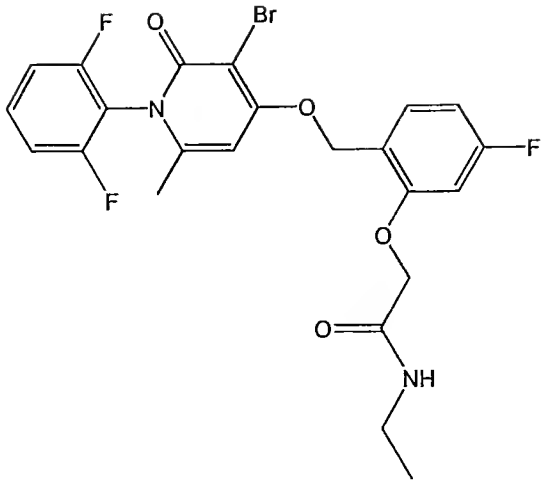


Prepared using a procedure similar to that used in Step 5 of the synthesis of Example 643. ^{1}H NMR (DMSO-d_6/ 400MHz) δ7.92 (m, 1H), 7.67 (s, 1H), 7.54 (m, 2H), 7.12 (m, 2H), 6.71 (s, 1H), 5.37 (s, 2H), 4.31 (d, 2H, J = 6.4 Hz), 2.40 (m, 1H), 2.00 (s, 3H), 1.88 (s, 3H), 0.56 (m, 2H), 0.33 (m, 2H). ESHRMS m/z 558.0988 and 560.0981 (M+H calculated for $C_{26}H_{26}BrFN_3O_5$ requires 558.1034 and 560.1018).

Step 4:

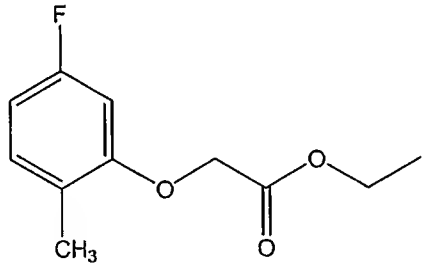
Prepared using a procedure similar to that used in the preparation of Example 643. ^{1}H NMR (CD_3OD/ 400MHz) δ7.85 (m, 1H), 7.54 (m, 3H), 7.14 (m, 1H), 7.03 (m, 1H), 6.69 (s, 1H), 5.41 (s, 2H), 4.48 (s, 2H), 2.89 (s, 3H), 2.48 (m, 1H), 2.08 (s, 3H), 1.99 (s, 2H), 0.70 (m, 2H), 0.47 (m, 2H). ESHRMS m/z 571.1348 and 573.1355 (M+H calculated for $C_{27}H_{29}BrFN_4O_4$ requires 571.1351 and 573.1335).

Example 652



3-[3-bromo-4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid

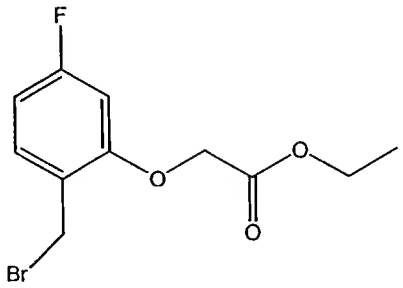
Step 1: Preparation of ethyl (5-fluoro-2-methylphenoxy)acetate.



To a solution of 5-fluoro-2-methylphenol (1.00 g, 7.93 mmol) and ethylbromoacetate (1.59 g, 9.51 mmol) in DMF (15 mL) was added K_2CO_3 (1.10 g, 7.93 mmol). After 30min at RT, DMF was removed by distillation. The crude product was washed with 5% citric acid (30 mL) and water (30 mL), extracted in DCM (3 x 20 mL), dried over Na_2SO_4, filtered, concentrated, and dried in vacuo. Desired product obtained as yellow oil (1.30 g, 77%). ^1H NMR (CD_3OD/ 400MHz) δ7.09 (t, 1H, J = 8.8 Hz), 6.58 (m, 1H), 6.56 (m, 1H), 4.71 (s, 2H), 4.23 (q, 2H, J = 7.2

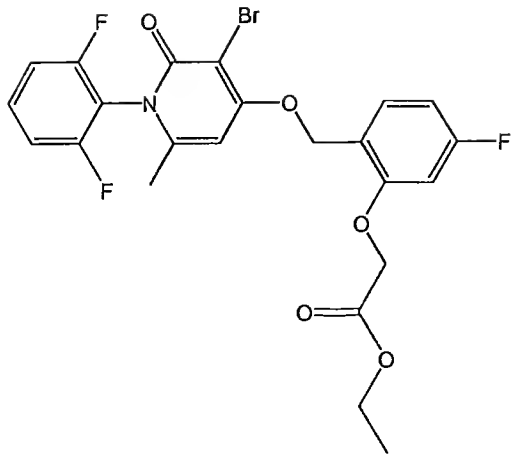
Hz), 2.18 (s, 3H), 1.27 (t, 3H, J = 7.2 Hz). ESHRMS m/z 212.0847 (M+H calculated for $C_{11}H_{13}FO_3$ requires 212.0849).

Step 2: Preparation of ethyl [2-(bromomethyl)-5-fluorophenoxy]acetate.



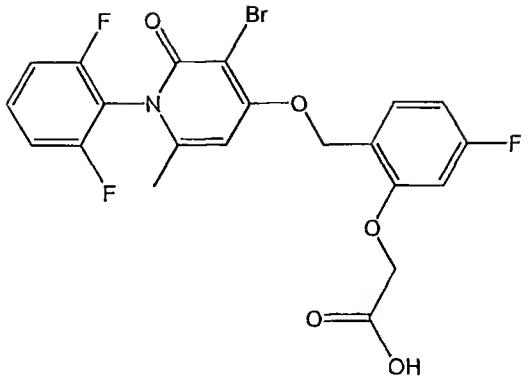
A solution of ethyl (5-fluoro-2-methylphenoxy)acetate (from Step 1) (0.65 g, 3.06 mmol), NBS (0.65 g, 3.68 mmol), and benzoyl peroxide (0.05 g, 0.21 mmol) in CCl4 (7.0 mL) were refluxed at 90°C for 2.5h. Additional NBS (0.16 g, 0.92 mmol) added, and reaction continued overnight. Solid filtered and filtrate concentrated onto silica gel. Purified by flash column chromatography using hexane and 2.5% EtOAc/hexane as eluent. Product obtained as yellow liquid (0.27 g, 30%). ^1H NMR (CD_3OD/ 400MHz) δ7.37 (m, 1H), 6.69 (m, 2H), 4.80 (s, 2H), 4.60 (s, 2H), 4.23 (q, 2H, J = 7.2 Hz), 1.27 (t, 3H, J = 7.2 Hz).

Step 3: Preparation of ethyl [2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorophenoxy]acetate.



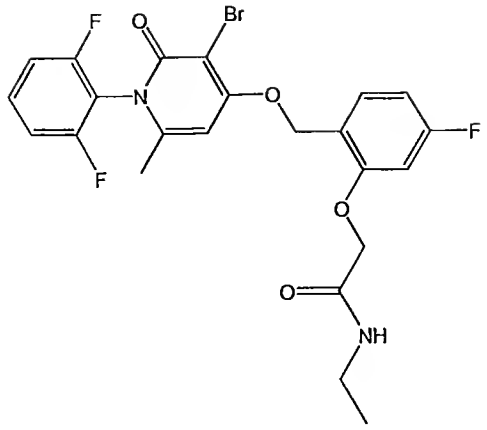
To a solution of ethyl [2-(bromomethyl)-5-fluorophenoxy]acetate (from Step 2) (0.59 g, 2.03 mmol) and 3-bromo-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.61 g, 1.93 mmol) in DMF (3.0 mL) was added K_2CO_3 (0.34 g, 2.43 mmol). After 2h at RT, DMF was removed by distillation. The crude product was washed with 5% citric acid, extracted in DCM, dried over Na_2SO_4, filtered, and concentrated onto silica gel. Purified by flash column chromatography using 50% EtOAc/hexane as the eluent. Obtained product as a pale yellow solid (0.45 g, 42%). ^1H NMR (CD_3OD/400MHz) δ7.21 (q, 3H, J = 8.4 Hz), 6.80 (m, 2H), 6.69 (s, 1H), 6.15 (s, 1H), 5.40 (s, 2H), 4.84 (s, 2H), 4.23 (q, 2H, J = 6.8 Hz), 2.08 (s, 3H), 1.26 (t, 3H, J = 6.8 Hz). ESHRMS m/z 526.0446 and 528.0414 (M+H calculated for $C_{23}H_{20}BrF_3NO_5$ requires 526.0471 and 528.0454).

Step 4: Preparation of [2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorophenoxy]acetic acid.



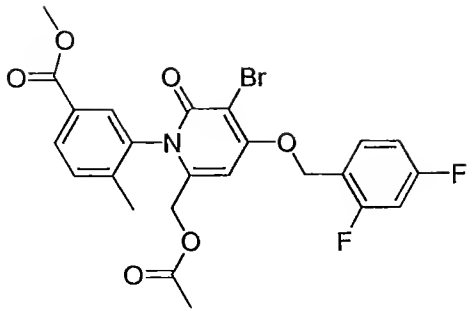
A solution of ethyl [2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorophenoxy]acetate (from Step 3) (0.62 g, 1.18 mmol), 1.5 N NaOH solution in 1:1 MeOH:water (1.2 mL, 1.77 mmol), and THF (1.2 mL) were refluxed at 60°C for 1h. The solution was concentrated on a rotary evaporator, cooled, and 5% citric acid added. The solid precipitate was filtered and dried in vacuo. Product obtained as a pale yellow solid (0.35 g, 60%). ^{1}H NMR (CD_3OD/ 400MHz) δ7.59 (m, 1H), 7.49 (m, 1H), 7.22 (m, 2H), 6.75 (m, 2H), 6.72 (s, 1H), 5.43 (s, 2H), 4.66 (s, 2H), 2.07 (s, 3H). ESHRMS m/z 498.0143 and 500.0186 (M+H calculated for $C_{21}H_{16}BrF_3NO_5$ requires 498.0158 and 500.0141).

Step 5: Preparation of 2-[2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorophenoxy]-N-ethylacetamide.



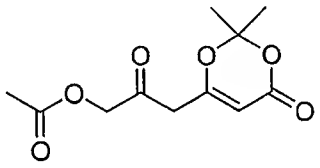
To a cooled (-10°C) solution of [2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorophenoxy]acetic acid (from Step 4) (0.15 g, 0.30 mmol) in DMA (2.0 mL) was added 4-methylmorpholine (0.04 mL, 0.36 mmol) and isobutyl chloroformate (0.05 mL, 0.36 mmol). Ethylamine (0.04 mL, 0.45 mmol) was added after 20 minutes. DMF removed by distillation after 1h. Crude product purified by preparatory HPLC. Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (30 mL) and extracted in DCM (3 x 25 mL). The organic extracts were dried over Na_2SO_4, filtered, concentrated, and dried in vacuo to give a white solid (0.080 g, 51%). ^1H NMR (CD_3OD/ 400MHz) δ7.60 (m, 1H), 7.53 (t, 1H, J = 8.0 Hz), 7.23 (t, 2H, J = 8.4 Hz), 6.82 (m, 2H), 6.71 (s, 1H), 5.42 (s, 2H), 4.61 (s, 2H), 3.31 (q, 2H, J = 6.4 Hz), 2.10 (s, 3H), 1.09 (t, 3H, J = 7.2 Hz). ESHRMS m/z 525.0616 and 527.0568 (M+H calculated for $C_{23}H_{21}BrF_3N_2O_4$ requires 525.0631 and 527.0614).

Example 653



methyl 3-[6-[(acetyloxy)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-4-methylbenzoate.

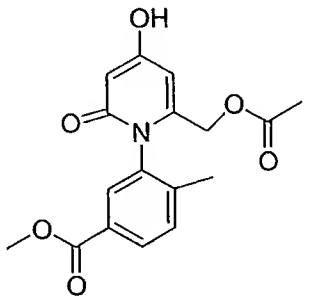
Step 1: Preparation of 3-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-2-oxopropyl acetate.



A solution of 2,2,6-trimethyl-4H-1,3-dioxin-4-one (20g, 141 mmol) in dry THF (400 mL) was cooled to -78 °C. To this solution was slowly added a LiHMDS (1M-THF, 160 mL, 160 mmol). The resulting solution was maintained at -78°C with stirring for 30 min. To the reaction mixture was added acetoxy acetylchloride (17 mL, 160 mmol) and the resulting mixture was maintained at -78 °C for at 1h. The reaction was then allowed to slowly warm to rt and stir for an additional 1h. The reaction was then quenched with addition of a 1N solution of ammonium chloride. The layers were sperated and the aqueous layer was extracted with ethyl acetate (5x). The organics were combined, dried, and concentrated in vacuo. The crude product was purified using a medium pressure liquid chromatography biotage system. Elution with hexanes-ethyl acetate (3:1) gave 13.1 g (38%) of a red-brown oil. The

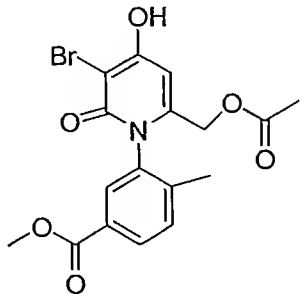
product looks clean by NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (s, 1H), 4.75 (s, 2H), 3.41 (s, 2H), 2.22 (s, 3H), 1.75 (s, 6H).

Step 2: Preparation of methyl 3-[6-[(acetyloxy)methyl]-4-hydroxy-2-oxopyridin-1(2H)-yl]-4-methylbenzoate.



To a 100 mL RBF containing methyl 3-amino,4-methylbenzoate (1.65g, 10 mmol) was added the enone from Step 1 (2.6g, 10.7 mmol). The mixture was then dissolved in toluene (40 mL), fitted with a reflux condenser, and placed in an oil bath preset to 115 °C. The mixture was heated to reflux for 1.5h. The reaction flask was removed from the oil bath and a catalytic amount of TFA (5-6 drops) was added. The reaction was placed back in the oil bath and heated to reflux for an additional 2h. The reaction was then allowed to cool to 0°C. The toluene was then removed under vacuum to give a thick brown residue. The residue was then dissolved in acetonitrile (10-15 mL) and allowed to stand. After 20-30 min a precipitate results which was filtered and washed with diethyl ether. After drying, an off-white solid (1.9g, 57% yield) was obtained. ^{1}H NMR (300 MHz, $DMSO_{-d6}$) δ 7.94 (dd, J = 7.8,1.5 Hz, 1H), 7.73 (s, 1H), 7.54 (d, J = 8.1 Hz, 1H), 6.19 (s, 1H), 5.73-5.71 (m, 1H), 4.47 (AB quar, J = 10.5 Hz, 2H), 3.87 (s, 3H), 2.09 (s, 3H), 1.91 (s, 3H). ES-HRMS m/z 332.1096 (M+H calcd for $C_{17}H_{18}NO_6$ requires 332.1129).

Step3: Preparation of methyl 3-[6-[(acetyloxy)methyl]-3-bromo-4-hydroxy-2-oxopyridin-1(2H)-yl]-4-methylbenzoate.

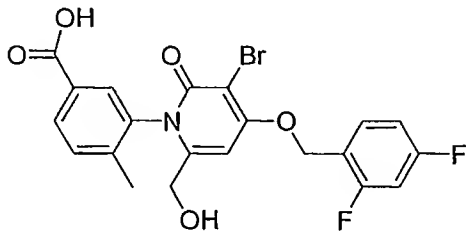


To a slurry of the phenol (2.5g, 7.5 mmol) in dry acetonitrile (50 mL), at rt, was added n-bromosuccinimide (1.33g, 7.5 mmol). The resulting homogeneous mixture was stirred at rt for 3h. The resulting precipitate was filtered and washed sequentially with acetonitrile and the diethyl ether. The product was dried in a vacuum oven to yield an off-white solid (2.5g, 81%). ^{1}H NMR (300 MHz, DMSO$_{-d6}$) δ 11.82 (s, 1H), 7.97 (dd, J = 7.8,1.5 Hz, 1H), 7.80 (d, J = 1.5 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 6.38 (s, 1H), 4.49 (AB quar, J = 13.8 Hz, 2H), 3.87 (s, 3H), 2.08 (s, 3H), 1.92 (s, 3H). ES-HRMS m/z 410.0225 (M+H calcd for $C_{17}H_{17}NBrO_6$ requires 410.0234).

Step 4: Preparation of the title compound. To a solution of the above phenol (2.5g, 6.0 mmol) in dry DMF (25 mL) was added solid potassium carbonate (804 mg, 6.0 mmol). To this mixture was then added, via syringe, 2,4-diflourobenzyl bromide (783 μL, 6.0 mmol). The resulting mixture was allowed to stir at rt overnight. The reaction was then poured into ice water and stirred vigorously. The resulting precipitate was filtered and washed sequentially with water and diethyl ether. The solid was dried in a vacuum oven to yield an off-white solid (3.3g, 99%). ^{1}H NMR (400 MHz, DMSO$_{-d6}$) δ 7.97 (dd, J = 7.6,1.2

Hz, 1H), 7.83 (d, J = 1.6 Hz, 1H), 7.71 (q, J = 8.8 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.37 (dt, J = 10.4, 2.4 Hz, 1H), 7.21 (dt, J = 8.4, 2.0 Hz, 1H), 6.90 (s, 1H), 5.40 (s, 2H), 4.57 (AB quar, J = 13.6 Hz, 2H), 3.86 (s, 3H), 2.07 (s, 3H), 1.90 (s, 3H). ES-HRMS m/z 536.0484 (M+H calcd for $C_{24}H_{21}NF_2BrO_6$ requires 536.0515).

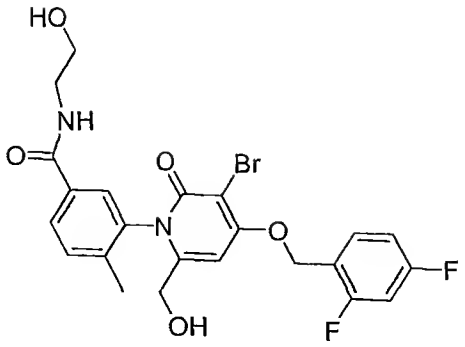
Example 654



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid.

To a stirred suspension, at rt, of the Example 643 (2.0g, 3.7 mmol) in THF (10 mL) was added a solution of 2.5N NaOH (3mL, 7.5 mmol). The resulting homogeneous solution was stirred for 2h. The reaction was judged complete and 1N HCl was added dropwise until a pH ~ 4 was obtained. The reaction was then diluted with CH_2Cl_2 (10 mL). The resulting precipitate was filtered with additional washing from CH_2Cl_2. The solid was dried in a vacuum oven to yield a pure white solid (1.8g, 99%). ^1H NMR (300 MHz, $DMSO_{-d6}$) δ 7.95 (dd, J = 7.8,1.8 Hz, 1H), 7.74-7.66 (m, 2H), 7.54 (d, J = 8.1 Hz, 1H), 7.37 (dq, J = 7.8, 2.7 Hz, 1H), 7.24-7.17 (m, 1H), 6.72 (s, 1H), 5.39 (s, 2H), 3.83 (AB quar, J = 15.6 Hz, 2H), 2.02 (s, 3H). ES-HRMS m/z 480.0253 (M+H calcd for $C_{21}H_{17}NF_2BrO_5$ requires 480.0253).

Example 655

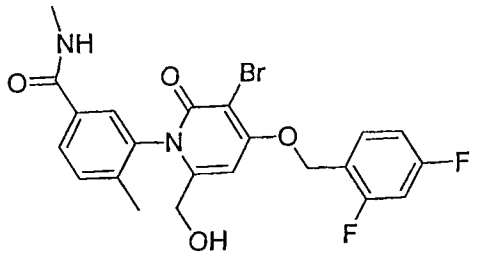


3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-2-oxopyridin-1(2H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide.

To a slurry of Example 654 (500mg, 1.04 mmol) in anhydrous CH_2Cl_2 was added Et_3N (218 µL, 1.56 mmol) and the resulting homogeneous mixture was stirred at rt. To this mixture was then added ethanolamine (70 µL, 1.14 mmol) via syringe. HOBt (155mg, 1.14 mmol) was then added followed by addition of EDC (217 mg, 1.14 mmol). The reaction was allowed to stir overnight at rt. The reaction was quenched by addition of a solution of 1N NH_4Cl. The biphasic mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (4X). The organics were combined, dried, and concentrated in vacuo. The resulting residue was purified by flash chromatography on a 16g Michele-Miller column. Elution with CH_2Cl_2-MeOH (10:1 → 12:1) resulted in obtaining the desired product as a viscous oil. The oil was then dissolved in a CH_3CN-Et_2O combination. After 5-10 minutes, a precipitate resulted which upon filtration and drying yielded a pure white solid (210 mg, 40%). ^1H NMR (300 MHz, $DMSO_{-d6}$) δ 8.46 (t, J = 5.2 Hz, 1H), 7.88 (dd, J = 8.0, 2.0 Hz, 1H), 7.72-7.65 (m, 2H), 7.50 (d, J = 8.4 Hz, 1H), 7.37 (dq, J = 9.6, 2.4 Hz, 1H), 7.20 (dq, J = 7.6, 1.6 Hz, 1H), 6.71 (s, 1H), 5.68 (t, J = 5.6 Hz, -OH), 5.40 (s, 2H), 4.73 (t, J = 5.6 Hz, -OH), 4.02 (dd, J = 16.4,

5.6 Hz, 1H), 3.70 (dd, J = 16.4, 5.6 Hz, 1H), 3.52-3.48 (m, 2H), 3.39-3.25 (m, 2H), 2.00 (s, 3H). ES-HRMS m/z 523.0674 (M+H calcd for $C_{23}H_{22}N_2F_2BrO_5$ requires 523.0675).

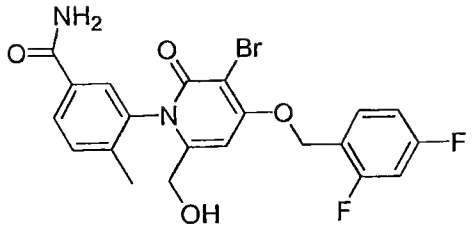
Example 656



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide.

The titled compound was prepared from the acid Example 654 (550 mg, 1.07 mmol) in a similar manner to the amide described above using EDC (245 mg, 1.28 mmol), HOBt (171 μL, 1.28 mmol), Et_3N (225 mL, 1.6 mmol), and 2.0M $MeNH_2$-THF (1.2 μL, 2.48 mmol). Following work-up with 1N NH_4Cl the product was precipitated out of the biphasic mixture after dilution with additional CH_2Cl_2 to give a white solid (250 mg, 51% yield). %). ^1H NMR (300 MHz, $DMSO_{-d6}$) δ 8.48 (quar, J = 4.5 Hz, 1H), 7.88 (dd, J = 8.1, 1.8 Hz, 1H), 7.72 (app quar, J = 6.6 Hz, 1H), 7.63 (d, J = 1.8 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.37 (dt, J = 10.2, 2.4 Hz, 1H), 7.20 (app dt, J = 8.4, 1.8 Hz, 1H), 6.74 (s, 1H), 5.71 (t, J = 5.4 Hz, 1H), 5.42 (s, 2H), 4.03 (dd, J = 13.8, 5.1 Hz, 1H), 3.72 (dd, J = 16.4, 5.1 Hz, 1H), 2.78 (d, J = 4.5 Hz, 3H), 2.02 (s, 3H). ES-HRMS m/z 493.0575 (M+H calcd for $C_{22}H_{20}N_2F_2BrO_4$ requires 493.0569).

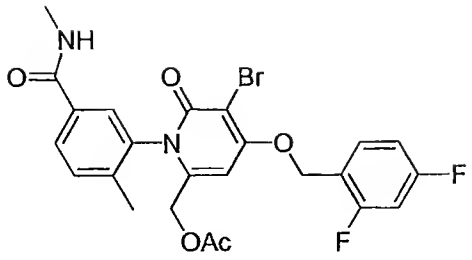
Example 657



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-2-oxopyridin-1(2H)-yl]-4-methylbenzamide.

To a stirred suspension, at rt, of the carboxylic acid Example 654 (400 mg, 0.80 mmol) in anhydrous THF (4 mL) was added 4-methylmorpholine (274 μL, 2.5 mmol). To the resulting heterogeneous solution was then added 2-Chloro-4,6-dimethyltriazine (170 mg, 1.0 mmol) and the mixture was allowed to stir for 1h at rt. Ammonium hydroxide solution (28-32%, 2 mL) was then added to the reaction and it was allowed to stir at rt overnight. The reaction was then worked up by diluting with H_20 (2-3 mL) and stirring vigorously. The resulting precipitate was filtered and washed with H2O and then diethyl ether. After drying with a vacuum oven an off-white solid (140 mg, 32%) was obtained. %). ^{1}H NMR (300 MHz, $DMSO_{-d6}$) δ 7.99-7.80 (m, 2H), 7.76 (m, 3H), 7.52 (d, J = 8.1 Hz, 1H), 7.43-7.39 (m, 2H), 7.52 (d, J = 8.1 Hz, 1H), 7.43-7.36 (m, 2H), 7.20 (dt, J = 8.7, 1.8 Hz, 1H), 6.74 (s, 1H), 5.41 (s, 2H), 4.02-3.62 (m, 2H), 2.03 (s, 3H). ES-HRMS m/z 479.0411 (M+H calcd for $C_{21}H_{18}N_2F_2BrO_4$ requires 479.0413).

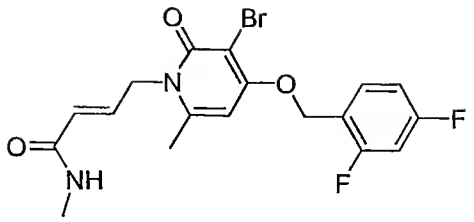
Example 658



(5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2-methyl-5-[(methylamino)carbonyl]phenyl}-6-oxo-1,6-dihydropyridin-2-yl)methyl acetate.

To a solution of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide, (225 mg, 0.50 mmol) stirred in CH_2Cl_2 was added pyridine (55 µL, 0.69 mmol). To the resulting homogeneous solution was then added acetic anhydride (47 µL, 0.51 mmol). The mixture was stirred at rt for 3h. Additional pyridine (150 µL, 1.8 mmol) and acetic anhydride (100 µL, 1.05 mmol) were then added and the reaction was allowed to stir overnight at rt. The reaction was then quenched with 1N $NHCl_4$ and diluted with CH_2Cl_2. The layers were separated and the organic layer was then extracted with CH_2Cl_2 (3X). The organics were then combined, dried, and concentrated in vacuo. The residue was then triturated with Et_2O and filtered to give (150 mg, 61%) an off-white solid. ^1H NMR (300 MHz, $DMSO_{-d6}$) δ 8.48 (br s, 1H), 7.87 (app d, J = 7.8 Hz, 1H), 7.74-7.69 (m, 2H), 7.52 (d, J = 7.5 Hz, 1H), 7.40 (app t, J = 8.1 Hz, 1H), 7.28-7.19 (m, 1H), 6.91 (s, 1H), 5.43 (s, 2H), 4.60 (s, 2H), 2.79 (s, 3H), 2.06 (s, 3H), 1.94 (s, 3H). ES-HRMS m/z 535.0676 (M+H calcd for $C_{24}H_{22}N_2F_2BrO_5$ requires 535.0675).

Example 659



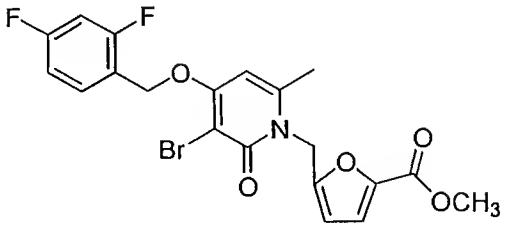
(2E)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-methylbut-2-enamide.

Step 1, (2E)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]but-2-enoic acid: The carboxylic acid compo was prepared by stirring the ester (900 mg, 2.1 mmol) in THF (10 mL). To this solution was added 1N NaOH (1 mL) and the resulting mixture was stirred at rt. After 2 h, additional NaOH (1 mL) was added to the reaction and then allowed to stir at rt overnight. The THF was then concentrated under vacuum. The remaining aqueous layer was then acidified to pH ~ 4 after which a white precipitate resulted. Filtration and drying under vacuum gave rise to a white solid (900 mg) that was used as in the next step.

The titled compound was prepared by stirring the above acid (480 mg, 1.16 mmol) in CH_2Cl_2 at rt. To this mixture was added sequentiallyEt_3N (244 μL), HOBt (188 mg, 1.4 mmol), $MeNH_2$ (2.0M-THF, 700 mL, 1.4 mmol), and finally EDC (266 mg, 1.4 mmol). The homogeneous mixture was then allowed to stir at rt overnight. The reaction was quenched with 1N HCl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4x). The organics were combined, dried, and concentrated in vacuo. The crude residue was triturated in CH_3CN-Et_2O combination and filtered to give a pure white solid (330 mg, 67%). ^{1}H-NMR ($DMSO_{d6}$/300 MHz) δ 8.20-7.90 (m, 1H), 7.68 (q, J = 8.4 hz, 1H); 7.37 (dt, J = 10.2, 2.4 Hz, 1H); 7.20 (dt, J = 15.6, 4.2 Hz, 1H); 6.60 (s, 1H), 5.63 (d, J = 15.6 Hz, 1H),

5.31 (s, 2H), 4.81 (d, J = 2.7 Hz, 2H), 3.33 (d, J = 6.9 Hz, 1H), 2.61 (d, J = 4.8 Hz, 3H), 2.37 (s, 3H). ES-HRMS m/z 427.0493 (M + H calcd for $C_{18}H_{18}BrF_2N_2O_3$ = 427.0463).

Example 660

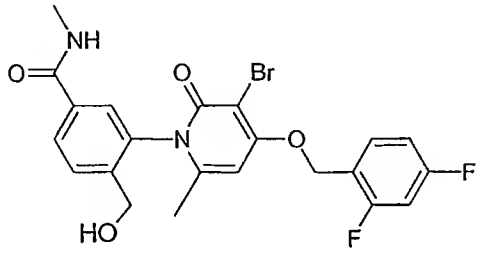


methyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-2-furoate

Step 1: To a room temperature suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (330.1 mg, 1.00 mmol)) and NaH (48.0 mg, 2.0 mmol) in THF (1.6 mL) was added methyl-5-chloromethyl-2-furate (400 mg, 2.30 mmol). The resulting suspension was stirred and heated to 68 °C for 8 hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then diluted with ammonium chloride (saturated aqueous solution, 10 mL) and water (100 mL). This resulting emulsion was then extracted with with ethyl acetate (3 X 300 mL). The resulting organic extract was separated, Na_2SO_4 dried, and concentrated. The resulting dark residue was subjected to SiO_2 chromatography with ethyl acetate/hexanes (3:7) to furnish a solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (app q, J = 8.2 Hz, 1H), 7.07 (d, J = 3.5 Hz, 1H), 6.93 (app dt, J = 8.4, 1.5 Hz, 1H), 6.84 (app ddd, J = 10.2, 8.7, 2.4 Hz, 1H), 6.53 (d, J = 3.4 Hz, 1H), 6.00 (s, 1H), 5.27 (s, 2H), 5.18 (s, 2H), 3.85 (s, 3H), 2.54 (s, 3H); LC/MS C-18 column, t_r = 2.64 minutes (5 to 95%

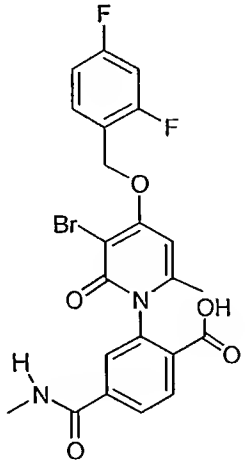
acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 468 (M+H). ES-HRMS m/z 468.0276 (M+H calcd for $C_{20}H_{17}BrF_2NO_5$ requires 468.0253).

Example 661



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-(hydroxymethyl)-N-methylbenzamide

Step 1: Preparation of 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl] benzoic acid .



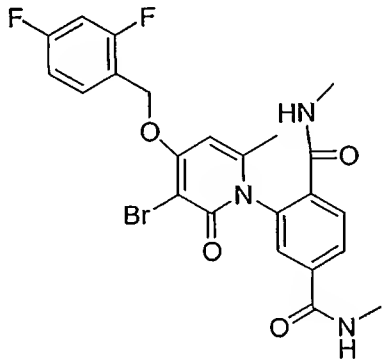
To a room temperature solution of methyl 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl]benzoate (1.05 g, 2.02 mmol) in THF

(10.0 mL) was added dropwise an aqueous solution of sodium hydroxide (3.0 M, 3.5 mL, 10 mmol). The reaction was then heated to 60 °C for 8.0 hours. The resulting suspension was then diluted with 500 mL of ethyl acetate and neutralized with an aqueous solution of hydrochloric acid (2.0 N, 5.0 mL, 10 mmol). The resulting biphasic solution was separated and the resulting aqueous layer was further extracted with ethyl acetate (2 X 200 mL). The resulting combined organic extracts were Na_2SO_4 dried, filtered and concentrated in vacuo to a volume of 50 mL. At this time a white solid began to form and the resulting solid suspension was allowed to sit until precipitation appeared to stop (approximately 1.0 hour). The precipitate was collected and dried in vacuo (1.0 mm Hg) to furnish the solid acid as an intermediate (806 mg, 78 %). ^1H NMR (400 MHz, d_7-DMF) δ 13.19 (s, 1H), 8.63 (app d, J = 4.5 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.00 (dd, J = 8.0, 1.6 Hz, 1H), 7.71-7.67 (m, 2H), 7.34 (app dt, J = 9.6, 1.6 Hz, 1H), 7.16 (app dt, J = 8.7, 1.8 Hz, 1H), 6.66 (s, 1H), 5.33 (s, 2H), 3.29 (s, 3H), 1.92 (s, 3H); LC/MS C-18 column, t_r = 2.15 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 507 (M+H). ES-HRMS m/z 507.0344 (M+H calcd for $C_{22}H_{18}BrF_2N_2O_5$ requires 507.0362).

Step 2: Preparation of the title compound . To a 0 °C solution of 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl] benzoic acid (500 mg, 0.986 mmol) in THF (6.8 mL) was added dropwise a solution of borane-dimethyl sulfide complex (THF solution, 2.0 M, 2.0 mL, 4.0 mmol). The internal temperature of the reaction was never allowed to exceed 0 °C. The resulting solution was maintained for 4.0 hours, at which time the

cooling bath was removed and the reaction was maintained at room temperature for an additional two hours. Next, a solution of ammonium chloride (saturated aqueous, 300 mL) was added. The resulting emulsion was extracted with ethyl acetate (3 X 300 mL) and the resulting organic extracts were separated, Na_2SO_4 dried, and concentrated in vacuo to a residue that was subjected to SiO_2 chromatography with ethyl acetate/hexanes (6:4) to furnish a solid (392 mg, 81 %). ^1H NMR (400 MHz, d_4-MeOH) δ 7.96 (dd, J = 8.0, 1.9 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.65 (app q, J = 8.0 Hz, 1H), 7.58 (d, J = 1.7 Hz, 1H), 7.05 (app t, J = 8.5 Hz, 2H), 6.64 (s, 1H), 5.36 (s, 2H), 4.35 (AB-q, J = 14.1 Hz, Δ= 60.8 Hz, 2H), 2.90 (s, 3H), 2.03 (s, 3H); LC/MS C-18 column, t_r = 2.16 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 493 (M+H). ES-HRMS m/z 493.0590 (M+H calcd for $C_{22}H_{20}BrF_2N_2O_4$ requires 493.0596).

Example 662

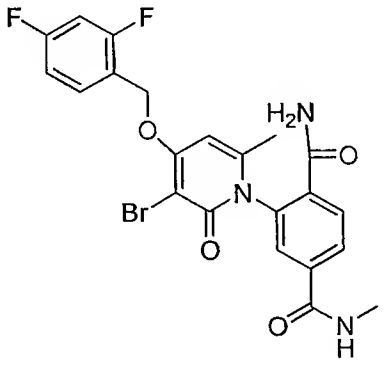


2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,N'-dimethylterephthalamide

Step 1: To a room temperature solution of 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-

[(methylamino)carbonyl] benzoic acid (500 mg, 0.986 mmol) in DMF (5.0 mL) was added 1-(3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride (EDC-HCl, 350.0 mg, 1.83 mmol) and 1-hydroxy-benzotriazole (HOBT, 100.0 mg, 0.74 mmol) sequentially. To this resulting suspension was then added a solution of methylamine (2.0 M THF, 1.0 mL, 2.0 mmol). The reaction was stirred for 16.0 hours, at which time the reaction was diluted with ethyl acetate (600 mL). The mixture was washed with (3 X 200 mL) of water and the organic extract was separated, Na_2SO_4 dried, and concentrated in vacuo to a volume of approximately 60 mL. At this time a solid precipitate formed and was collected to furnish (289 mg, 56 %). ^1H NMR (300 MHz, d_4-MeOH) δ 8.06 (br d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.73 (s, 1H), 7.70 (app q, J = 7.4 Hz, 1H), 7.09 (app t, J = 8.0 Hz, 2H), 6.65 (s, 1H), 5.39 (s, 2H), 2.96 (s, 3H), 2.79 (s, 3H), 2.13 (s, 3H); LC/MS C-18 column, t_r = 2.13 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 520 (M+H). ES-HRMS m/z 520.0700 (M+H calcd for $C_{23}H_{21}BrF_2N_3O_4$ requires 520.0678).

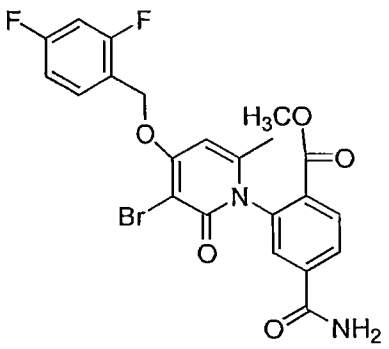
Example 663



2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-4-methylterephthalamide

Step 1: To a room temperature suspension of 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl] benzoic acid (302 mg, 0.595 mmol) in THF (1.8 mL) was added 2-chloro-4,6 dimethoxy-1,3,5 triazine (140.5 mg, 0.800 mmol) and N-methyl morpholine (NMM, 184 mg, 1.824 mmol) sequentially. The resulting solution was matured for 2 hours and then a saturated aqueous solution of ammonium hydroxide (0.60 mL) was added. The reaction was allowed to continue for 1 additional hour at which time a precipitate formed which was collected, washed with 20 mL of diethyl ether, and dried in vacuo to furnish a solid (201 mg, 66 %). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.59 (br d, J = 8.0, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H), 7.72 (d, J = 9.0, 1H), 7.69-7.64 (m, 2H), 7.39-7.31 (m, 1H), 7.19 (app t, J = 8.0 Hz, 1H), 6.60 (s, 1H), 5.31(s, 2H), 3.85 (s, 1H), 2.78 (br d, J = 8.0 Hz, 3H), 1.96 (s, 3H); LC/MS C-18 column, t_r = 2.20minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 506 (M+H). ES-HRMS m/z 506.0550 (M+H calcd for $C_{22}H_{19}BrF_2N_3O_4$ requires 506.0522).

Example 664

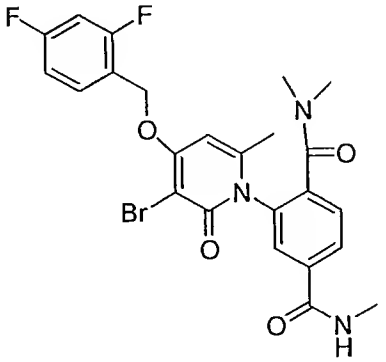


methyl 4-(aminocarbonyl)-2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate

Step 1: To a room temperature solution of 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-(methoxycarbonyl)benzoic acid (3.01 g, 9.93 mmol) in DMF (20 mL) was added 1-(3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride (EDC-HCl, 2.00 g, 10.4 mmol) and 1-hydroxy-benzotriazole (HOBT, 50.0 mg, 0.367 mmol) sequentially. To this resulting suspension was then added a solution of ammonia (0.5 M 1,4 dioxane, 30.0 mL, 15.0 mmol). The reaction was stirred for 16.0 hours until complete consumption of starting material was seen by LCMS analysis. At this time the reaction vessel was placed on a roto-evaporator at 30 mm Hg vacuum and maintained at 30 °C for 30 minutes to strip off any residual ammonia from the reaction mixture. The reaction vessel was removed from the roto-evaporator and subsequently charged with solid N-bromosuccinimide (1.790 g, 10.06 mmol) and the resulting reddish solution was stirred for 3.0 hours. At this time the reaction was charged with K_2CO_3 (3.00 g, 21.7 mmol) and 2,4 difluorobenzyl bromide (1.95 mL, 15.2 mmol). The resulting suspension was stirred for 16.0 hours. At this time the reaction suspension was diluted with water (400 mL) and extracted with ethyl acetate (3 X 300 mL). The organic extracts were separated, Na_2SO_4 dried, and concentrated to a residue that was subjected to SiO_2 chromatography using ethyl acetate/hexanes/methanol (6:3.5:0.5) to furnish an off white solid (1.09 g, 21%). ^1H NMR (400 MHz, d_4-MeOH) δ 8.21 (dd, J = 8.5, 1.5 Hz, 1H), 8.09 (dd, J = 7.6, 2.0 Hz, 1H), 7.78 (br s, 1H), 7.65 (app q, J = 7.9 Hz, 1H), 7.03 (app t, J = 8.0 Hz, 2H), 6.63 (s, 1H), 5.37 (s, 2H), 3.75 (s, 3H), 2.02 (s, 3H); LC/MS C-18 column, t_r = 2.28 minutes (5 to 95%

acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 507 (M+H). ES-HRMS m/z 507.0385 (M+H calcd for $C_{22}H_{18}BrF_2N_2O_5$ requires 507.0362).

Example 665

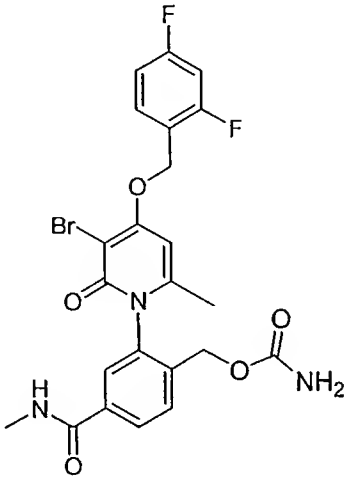


2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N^1,N^1,N^4-trimethylterephthalamide

Step 1: To a room temperature solution of 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl] benzoic acid (300 mg, 0.591 mmol) in DMF (1.8 mL) was added 1-(3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride (EDC-HCl, 190.0 mg, 1.0 mmol) and 1-hydroxy-benzotriazole (HOBT, 26.0 mg, 0.191 mmol) sequentially. To this resulting suspension was then added a solution of dimethylamine (2.0 M THF, 0.50 mL, 1.0 mmol). The reaction was stirred for 16.0 hours, at which time the reaction mixture was directly applied to SiO_2 chromatography with ethyl acetate/hexanes (6:4) to furnish a solid (206 mg, 65 %). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.01 (dd, J = 8.2, 1.5 Hz, 1H), 7.73 (app d, J = 8.1 Hz, 1H), 7.61 (app q, J = 7.2 Hz, 1H), 7.60 (app d, J = 9.5 Hz, 1H), 7.04 (app t, J = 8.0 Hz, 2H), 6.65 (s, 1H), 5.32 (s, 2H), 3.64 (s, 3H), 2.92 (s, 6H), 2.13 (s, 3H); LC/MS C-18 column, t_r = 2.20 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection

254 nm, at 50°C). ES-MS m/z 534 (M+H). ES-HRMS m/z 534.0820 (M+H calcd for $C_{24}H_{23}BrF_2N_3O_4$ requires 534.0835).

Example 666

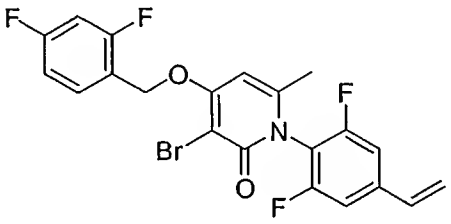


2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl]benzyl carbamate

Step 1: To a room temperature solution of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-(hydroxymethyl)-N-methylbenzamide (493 mg, 1.00 mmol) in methylene chloride (5.0 mL) was added a solution of trichloroacetyl isocyanate (toluene, 0.53 M, 1.9 mL, 1.0 mmol). The resulting solution was stirred for one hour until complete consumption of starting material by LCMS analysis. The reaction mixture was then directly applied to Al_2O_3 (0.5 g of activity type I) and the slurry was matured for three hours. At this time, the Al_2O_3 plug was flushed with ethyl acetate/methanol (95:5) and the resulting mother liquor was concentrated to a residue that was subjected to SiO_2 chromatography using ethyl acetate/hexanes/methanol (6:3.5:0.5) to furnish a white solid (396 mg, 74 %). ^1H NMR (300 MHz, d_4-MeOH) δ 8.00 (dd, J = 8.0, 1.7 Hz, 1H), 7.75 (d, J

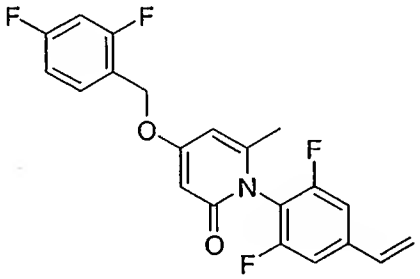
= 8.2 Hz, 1H), 7.72-7.64 (m, 2H), 7.09 (app t, J = 8.5 Hz, 2H), 6.69 (s, 1H), 5.40 (s, 2H), 4.85 (m, 2H), 2.90 (s, 3H), 2.10 (s, 3H); LC/MS C-18 column, t_r = 2.15 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 536 (M+H). ES-HRMS m/z 536.0617 (M+H calcd for $C_{23}H_{21}BrF_2N_3O_5$ requires 536.0627).

Example 667



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-vinylphenyl)-6-methylpyridin-2(1H)-one

Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-vinylphenyl)-6-methylpyridin-2(1H)- one .



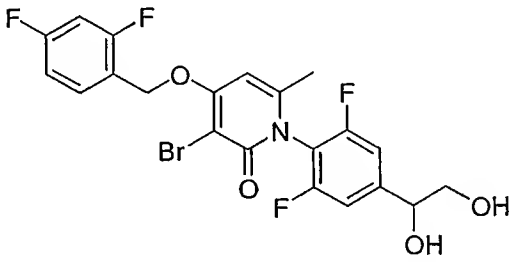
To a room temperature solution of 1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)- one (4.01 g, 9.06 mmol) in anhydrous THF (30mL) was added, sequentially, tributyl(vinyl)tin (5.00 g, 15.7 mmol) and tetrakis(tripheylphosphine)palladium (1.00 g, 0.865 mmol) under an argon stream. The reaction vessel was then equipped with a reflux condenser and the reaction system purged with an

argon flow. The resulting yellow solution was heated to 68 °C and stirred under a positive pressure of argon for 12.0 hours until complete disappearance of starting material by LCMS analysis. The reaction mixture was diluted with 300 mL of brine and extracted with ethyl acetate (3 X 300 mL). The organic extracts were separated, Na_2SO_4 dried, and concentrated in vacuo and the resulting dark residue was subjected to SiO_2 chromatography with ethyl acetate/hexanes (1:1) to furnish a yellowish solid (3.18 g, 90 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (app q, J = 8.0 Hz, 1H), 7.08 (app d, J = 8.3 Hz, 2H), 6.90 (app t, J =7.2 Hz, 1H), 6.85 (app t, J = 7.4 Hz, 1H), 6.63 (dd, J = 17.5, 10.9 Hz, 1H), 5.96 (app d, 15.8 Hz, 1H), 5.94 (app d, J = 15.8 Hz, 1H), 5.79 (d, J = 17.4 Hz, 1H), 5.43 (d, J = 10.9 Hz, 1H), 5.01 (br s, 2H), 1.99 (s, 3H); LC/MS C-18 column, t_r = 2.93 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 390 (M+H). ES-HRMS m/z 390.1095 (M+H calcd for $C_{21}H_{16}F_4NO_2$ requires 390.1112).

Step 2: To a briskly stirred room temperature solution of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-vinylphenyl)-6-methylpyridin-2(1H)- one (721 mg, 1.85 mmol) in methylene chloride (10 mL) was added solid N-bromosuccinimide (330 mg, 1.86 mmol) and the resulting reddish solution was stirred for 10 minutes. At this time the reaction was diluted with ethyl acetate (100 mL) and washed with sodium sulfite (5 % aqueous solution, 50 mL) The resulting organic extracts were Na_2SO_4 dried, filtered, and concentrated in vacuo to approximately 50 mL volume. The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected and dried at 1 mm Hg vacuum to provide a solid (610 mg, 70 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (app q, J = 8.0 Hz, 1H), 7.09 (app d, J

= 8.3 Hz, 2H), 6.95 (app t, J =7.2 Hz, 1H), 6.87(app t, J = 7.4 Hz, 1H), 6.62 (dd, J = 17.5, 10.9 Hz, 1H), 6.12 (s, 1H), 5.81 (d, J = 17.4 Hz, 1H), 5.43 (d, J = 10.9 Hz, 1H), 5.25 (br s, 2H), 2.07 (s, 3H); LC/MS C-18 column, t_r = 3.17 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 468 (M+H). ES-HRMS m/z 468.0249 (M+H calcd for $C_{21}H_{15}BrF_4NO_2$ requires 468.0217).

Example 668

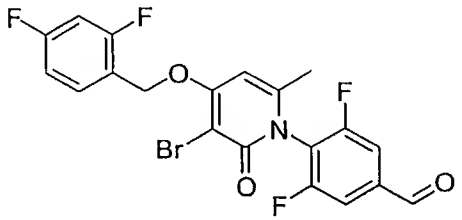


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(1,2-dihydroxyethyl)-2,6-difluorophenyl]-6-methylpyridin-2(1H)-one

Step 1: Preparation of the title compound . To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-vinylphenyl)-6-methylpyridin-2(1H)-one (408.0 mg, 0.871 mmol) in water/acetone 1:3 (8.0 mL) was added, sequentially, N-methyl morpholine oxide (268.0 mg, 2.29 mmol) and osmium tetroxide (4 % water solution, 0.25 mL or approximately 10 mg, 0.039 mmol). The resulting solution was stirred for 8 hours until complete consumption of starting material by LCMS analysis, and the reaction was concentrated in vacuo to one-
fourth original volume. The resulting solution was diluted with ethyl acetate (300 mL) and washed with water (2 X 100 mL). The organic extract was separated, Na_2SO_4 dried, and concentrated in vacuo and the resulting dark residue was subjected to SiO_2 chromatography with ethyl acetate/hexanes/

methanol (6:3.5:0.5) to furnish a solid (389 mg, 88 %). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.62 (app q, J = 8.0 Hz, 1H), 7.26 (dd, J = 9.6, 4.5 Hz, 2H), 7.04 (app t, J = 8.6 Hz, 2H), 6.67 (s, 1H), 5.36 (s, 2H), 4.75 (app t, J = 5.6 Hz, 1H), 3.68-3.61 (m, 2H), 2.11 (s, 3H); LC/MS C-18 column, t_r = 2.26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 502 (M+H). ES-HRMS m/z 502.0247 (M+H calcd for $C_{21}H_{17}BrF_4NO_4$ requires 502.0272).

Example 669

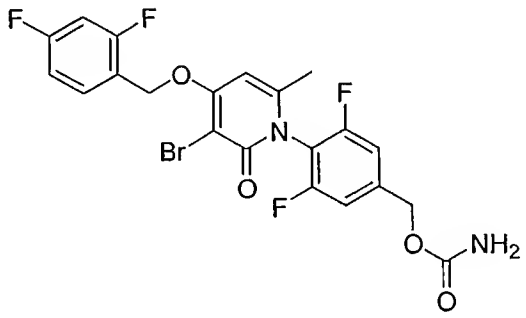


4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzaldehyde

Step 1: Preparation of the title compound . To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(1,2-dihydroxyethyl)-2,6-difluorophenyl]- 6-methylpyridin-2(1H)-one (310 mg, 0.615 mmol) in toluene (3.0 mL) was added lead(IV) acetate (443 mg, 1.63 mmol). The resulting dark brown solution was stirred for one hour until complete consumption of starting material by LCMS analysis. The reaction mixture was then diluted with ethyl acetate (100 mL), water washed (3 X 100 mL), and brine washed (3 X 30 mL). The resulting organic extract was separated, Na_2SO_4 dried, and concentrated. The resulting dark residue was subjected to SiO_2 chromatography with ethyl acetate/ hexanes (1:1) to furnish a light yellow solid (269 mg, 93 %). Caution, product is easily air oxidized. ^{1}H NMR (300 MHz, d_4-MeOH) δ 10.05 (s, 1H), 7.68 (app q, J = 7.2 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.05 (app t, J =

8.2 Hz, 2H), 6.73 (s, 1H), 5.40 (s, 2H), 2.15 (s, 3H); LC/MS C-18 column, t_r = 2.72 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 470 (M+H). ES-HRMS m/z 470.0049 (M+H calcd for $C_{20}H_{13}BrF_4NO_3$ requires 470.0009).

Example 670



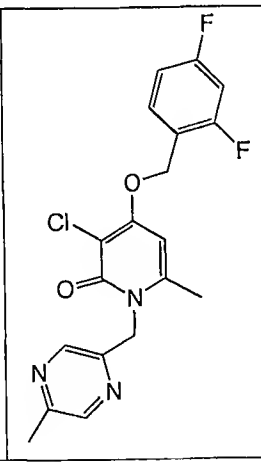
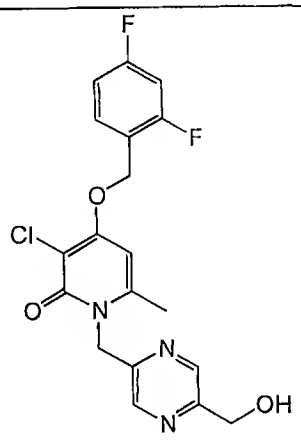
4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl carbamate

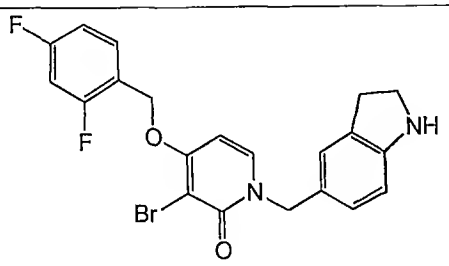
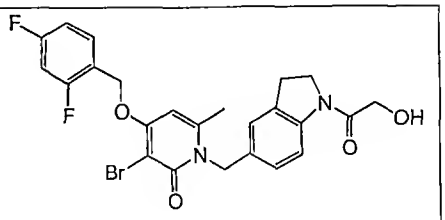
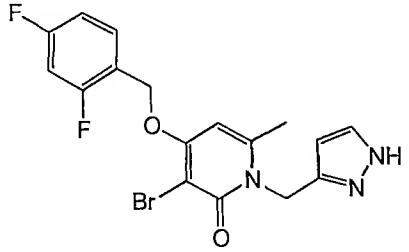
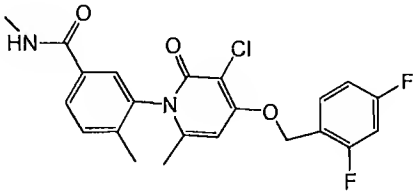
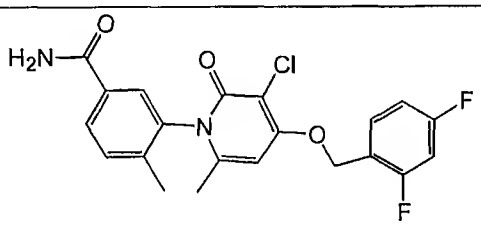
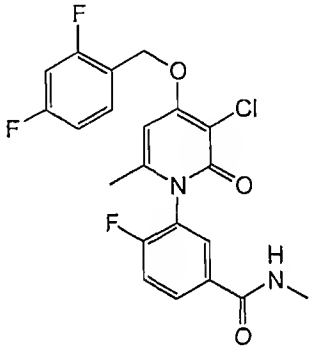
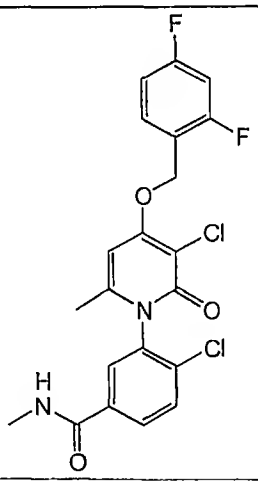
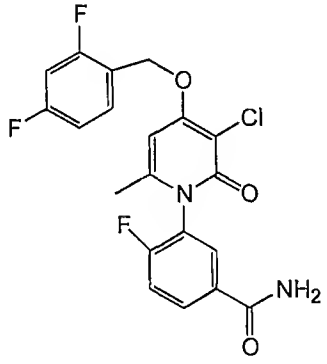
Step 1: To a room temperature solution of 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzaldehyde (220 mg, 0.468 mmol) in methanol (10 mL) was added solid sodium borohydride (60.0 mg, 1.58 mmol). The resulting solution evolved gas for approximately 0.5 minute and was stirred for 10 additional minutes until complete consumption of starting material by LCMS analysis. The reaction was then diluted with saturated aqueous solution of ammonium chloride (10 mL) and extracted with ethyl acetate (4 X 50 mL). The organic extract was separated, Na_2SO_4 dried, and concentrated to a residue. This resulting residue was then diluted with methylene chloride (5.0 mL) and a solution of trichloroacetyl isocyanate (toluene, 0.53 M, 1.0 mL, 0.53 mmol) was added. The resulting solution was stirred for one hour until complete consumption of starting material by LCMS

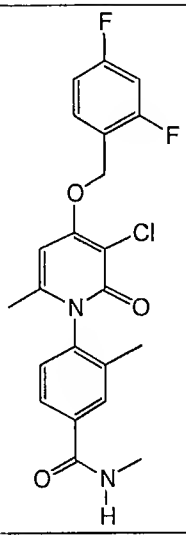
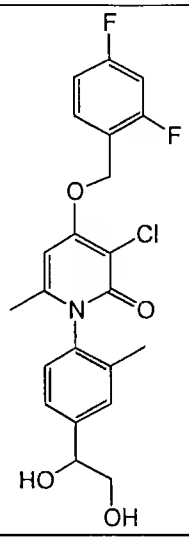
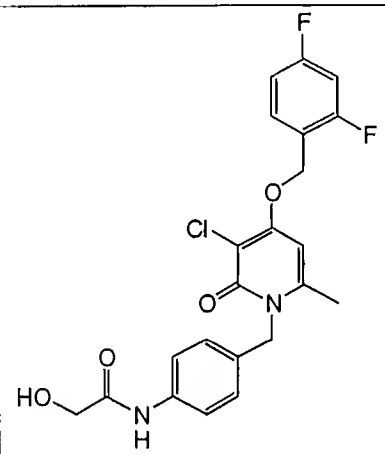
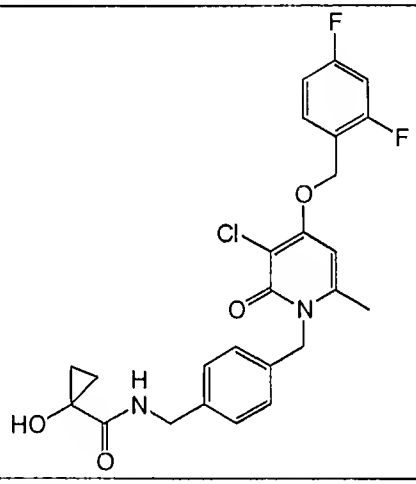
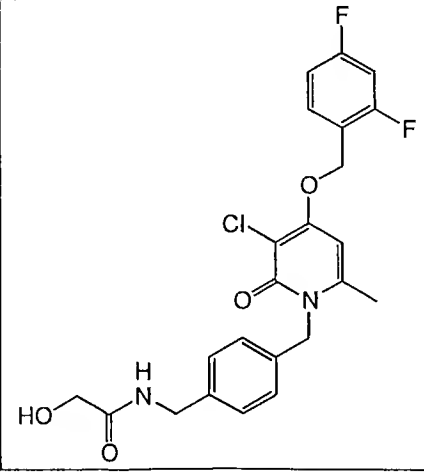
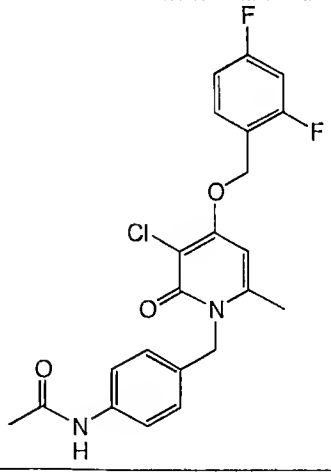
analysis. The reaction mixture was then directly applied to Al_2O_3 (0.5 g of activity type I) and the slurry was matured for three hours. At this time, the Al_2O_3 plug was flushed with ethyl acetate/methanol (95:5) and the resulting mother liquor was concentrated to a residue that was subjected to SiO_2 chromatography using ethyl acetate/hexanes/methanol (6:3.8:0.2) to furnish a white solid (181 mg, 75 %). ^1H NMR (400 MHz, d_4-MeOH) δ 7.63 (app q, J = 8.0 Hz, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.04 (app t, J = 8.1 Hz, 2H), 6.68 (s, 1H), 5.37 (s, 2H), 5.12 (m, 2H), 2.11 (s, 3H); LC/MS C-18 column, t_r = 2.54 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 515 (M+H). ES-HRMS m/z 515.0232 (M+H calcd for $C_{21}H_{16}BrF_4N_2O_4$ requires 515.0234).

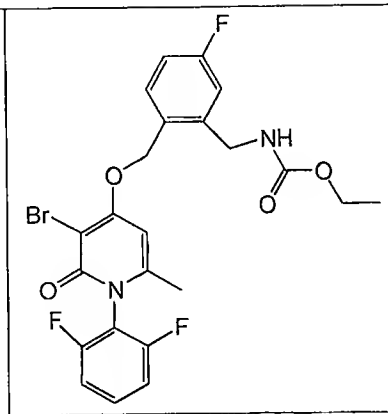
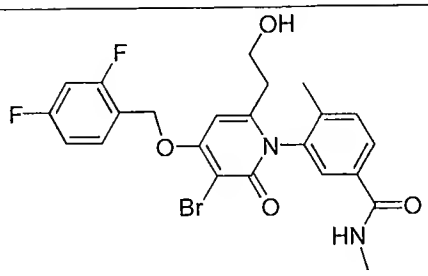
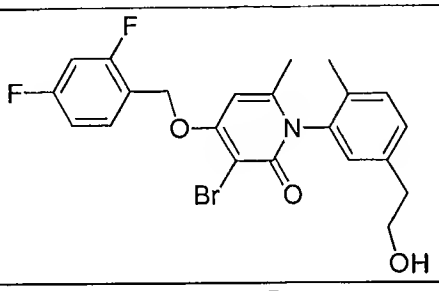
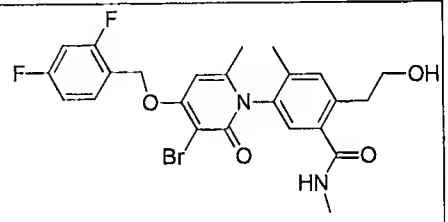
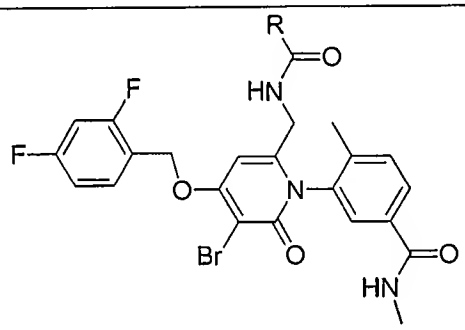
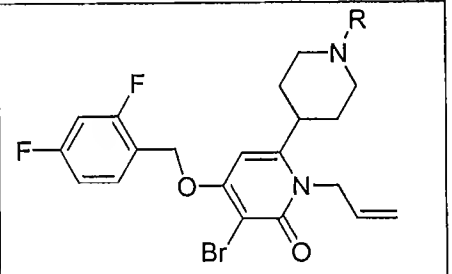
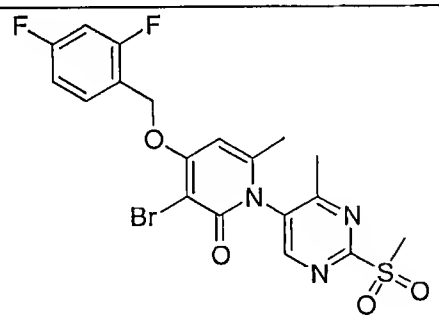
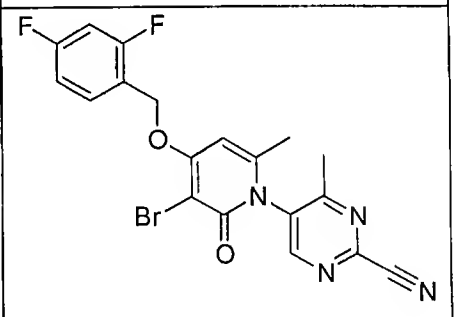
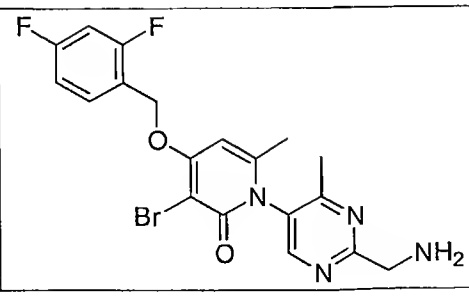
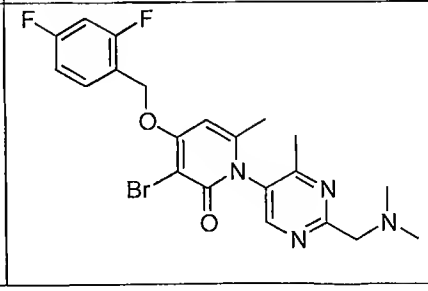
Example 671-687

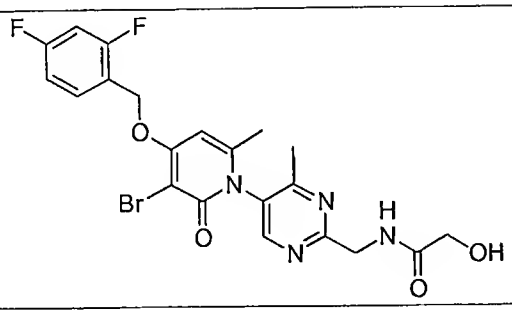
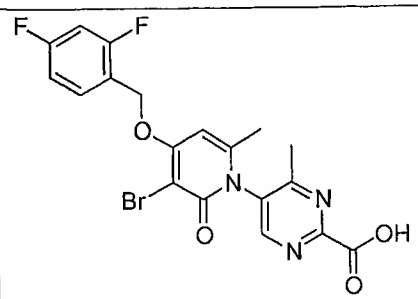
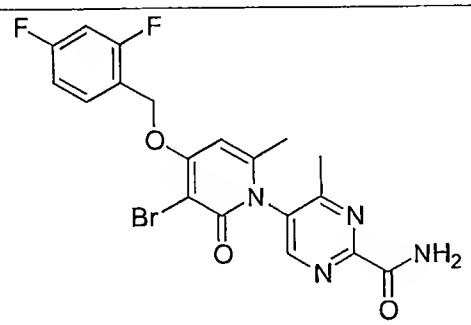
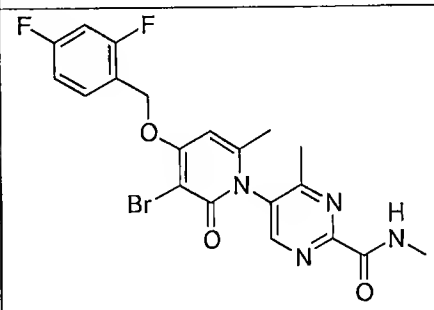
The following compounds are prepared essentially according to the procedures outlined in the schemes and the above examples

Example No.		Example No.	
Example 671		672	

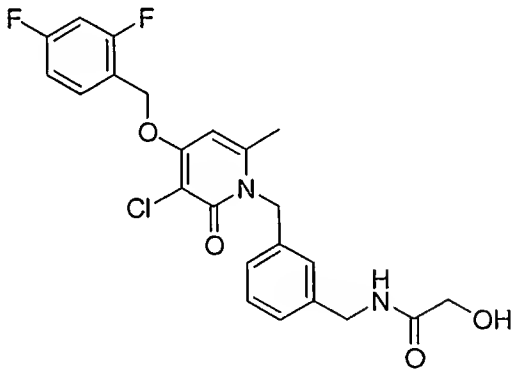
673		674	
675		676	
677		678	
679		680	

681		682	
683		684	
685		686	

687		688	
689		690	
691		692	
693		694	
695		696	

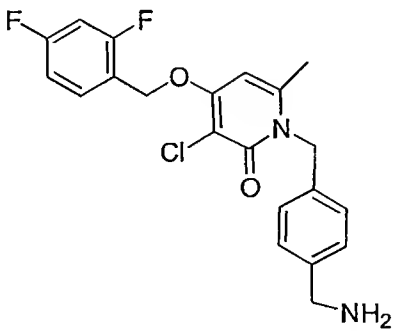
697		698	
699		700	

Example 701



N-(4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-2-hydroxyacetamide

Step 1. Preparation of 1-[4-(aminomethyl)benzyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one.



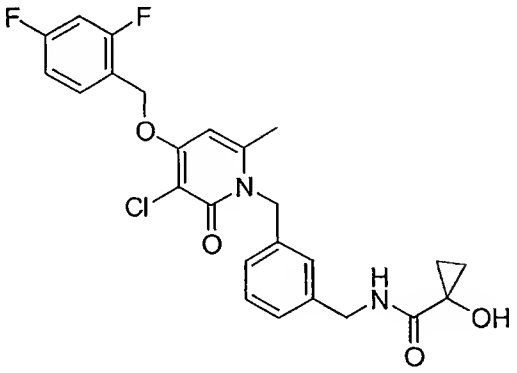
The compound of Example 606 (10.0 g, 23.38 mmol) was suspended in tetrahydrofuran (100 mL) and cooled in an ice-bath. Borane dimethyl sulfide (29.9 mL, 2.0 *M* in tetrahydrofuran, 59.7 mmol) was added. The resulting mixture was heated to reflux overnight and then cooled in an ice-bath. Additional borane dimethyl sulfide (5.85 mL, 2.0 *M* in tetrahydrofuran, 11.7 mmol) was added. The resulting mixtue was heated to reflux overnight and the cooled to room temperature. The flask was fitted with a distillation head and the reaction was partially concentrated. Additional borane dimethyl sulfide (5.85 mL, 2.0 *M* in tetrahydrofuran, 11.7 mmol) was added. The mixture was heated to reflux overnight and the cooled in an ice-bath. The reaction was quenched by the addition of 1.0 *N* HCl (75.0 mL) then partially concentrated. The aqueous layer was made alkaline with 2.5 *N* NaOH and a precipitate developed. The solid was collected by filtration washing with diethyl ether to give a pale purple solid (3.00 g, 32 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (*app* q, J = 7.9 Hz, 1H), 7.44 (d, J = 7.9 Hz, 2H), 7.32 (*app* dt, J = 2.4, 9.9 Hz, 1H), 7.14 (*app* dt, J = 1.9, 8.5 Hz, 1H), 7.13 (d, J = 7.9 Hz, 2H), 6.61 (s, 1H), 5.27 (s, 4H), 3.90 (s, 2H), 2.29 (s, 3H).

Step 2. Preparation of N-(4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzyl)-2-hydroxyacetamide.

Acetoxyacetic acid (1.46 g, 12.35 mmol) was dissolved in *N,N*-dimethylformamide (30 mL) and 1-Hydroxybenzotriazole (1.84 g, 13.59 mmol) was added followed by 4-methylmorpholine (2.04 mL, 18.53 mmol), 1-[4-(aminomethyl)benzyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (compound of step 1) (2.50 g, 6.18 mmol) and then 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.84 g, 14.83 mmol). The resulting mixture was stirred at room

temperature for 1 hour at which time the reaction was diluted with H_2O (100 mL). The reaction mixture was then extracted with ethyl acetate. The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated. Chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) provided a white foam. The resulting foam was dissolved in 10% aqueous methanol (20 mL). K_2CO_3 (0.653 g, 4.73 mmol) was added and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated and H2O (50 mL) was added. The resulting precipitate was collected by filtration washing with diethyl ether to give an off-white solid (1.34 g, 47%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (*app* q, J = 7.7 Hz, 1H), 7.27 (app t, J = 5.8 Hz, 1H), 7.12 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 8.1 Hz, 2H), 6.94-6.89 (m, 1H), 6.86-6.81 (m, 1H), 6.09 (s, 2H), 5.23 (s, 2H), 5.18 (s, 2H), 4.53 (t, J = 5.8 Hz, 1H), 4.33 (d, J = 5.9 Hz, 2H), 3.85 (d, J = 5.6 Hz, 2H), 2.30 (s, 3H). ES-HRMS *m/z* 463.1256 (M+H calcd for $C_{23}H_{22}ClF_2N_2O_4$ requires 463.1231).

Example 702

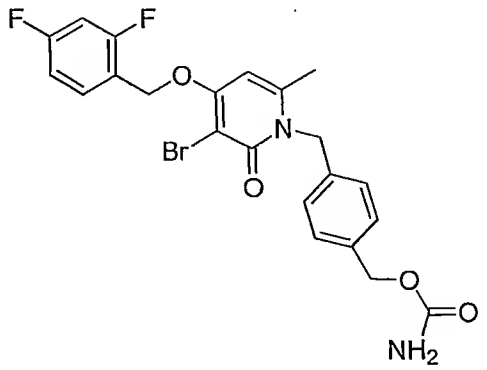


N-(4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-1-hydroxycyclopropanecarboxamide

Preparation of N-(4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzyl)-1-hydroxycyclopropanecarboxamide. 1-Hydroxy-1-cyclopropane-

carboxylic acid (1.26 g, 12.35 mmol) was dissolved in *N,N*-dimethylformamide (30 mL). 1-Hydroxybenzotriazole (1.84 g, 13.59 mmol) was added followed by 4-methylmorpholine (2.04 mL, 18.53 mmol), 1-[4-(aminomethyl)benzyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (Example 701, step 1) (2.50 g, 6.18 mmol) and then 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.84 g, 14.83 mmol). The resulting mixture was stirred at room temperature for 24 hours at which time the reaction was diluted with H_2O (100 mL). The reaction mixture was then extracted with ethyl acetate. The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated. Chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) provided a white foam. The resulting foam was dissolved in 10% aqueous methanol (20 mL) to provide an white foam (1.45 g, 48%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.46 (m, 1H), 7.34 (t, J = 5.9 Hz, 1H), 7.08 (d, J = 8.2 Hz, 2H), 6.92 (*app* d, J = 8.2 Hz, 2H), 6.92-6.89 (m, 1H), 6.86-6.81 (m, 1H), 6.11 (s, 1H), 5.22 (s, 2H), 5.18 (s, 2H), 4.30 (d, J = 5.9 Hz, 2H), 2.28 (s, 3H), 1.11 (*app* q, J = 4.1 Hz, 2H), 0.90 (*app* q, J = 4.1 Hz, 2H). ES-HRMS *m/z* 489.1420 (M+H calcd for $C_{25}H_{24}ClF_2N_2O_4$ requires 489.1387).

Example 703

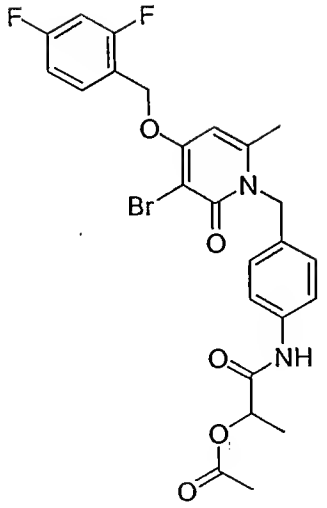


4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzyl carbamate

Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzyl carbamate

Compound of Example 206 (0.868 g, 1.93 mmol) was suspended in dichloromethane (7.0 mL). Trichloroacetyl isocyanate (4.00 mL, 0.53 *M* in toluene, 2.12 mmol) was added. The resulting mixture was stirred at room temperature for 3 hours then diluted with tetrahydrofuran (50 mL) and Al2O3 (5.0 g) was added and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through a pad of Celite® washing with methonal. The filtrate was then concentrated and the residue was redissolved in tetrahydrofuran (30 mL). Al_2O_3 (5.0 g) was added and the mixture was heated to 40 oC for 3 hours. After cooling to room temperature, the reaction was filtered through a pad of Celite ® washing with methanol. The filtrate was concentrated and the resulting solid was washed with diethyl ether to give an off-white solid (0.831 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (*app* q, J = 7.7 Hz, 1H), 7.25 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 8.2 Hz, 2H), 6.25 (*app* dt, J = 2.0, 8.3 Hz, 1H), 6.86-6.30 (m, 1H), 5.97 (s, 1H), 5.32 (s, 2H), 5.18 (s, 2H), 5.02 (s, 2H), 4.81 (br s, 2H), 2.25 (s, 3H). ES-HRMS *m/z* 493.0580 (M+H calcd for $C_{22}H_{20}BrF_2N_2O_4$ requires 493.0569).

Example 704

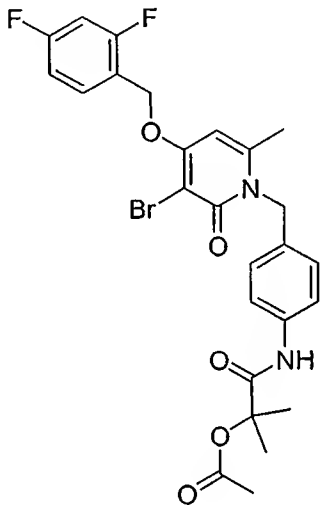


2-[(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}phenyl)amino]-1-methyl-2-oxoethyl acetate

To a reaction vessel (borosilicate culture tube) was added compound of Example 611 (0.300 g, 0.69 mmol) and dichloromethane (3.0 mL). A stock solution of *N*-methylmorpholine (0.30 M, 3.0 mL) was added and the parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 10 minutes. (S)-(-)-2-Acetoxypropionyl chloride (0.131 mL, 1.04 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature for 1.5 hours. At this time the reaction was diluted with dichloromethane (20 mL) and treated with approximately 2.1 g of polyamine resin (2.63 mmol/g) and approximately 3.8 g of methylisocyanate fucntionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature overnight. The reaction vessel was then opened and the solution Phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with dichloromethane (2 x 10 mL). The

filtrate was evaporated by blowing N_2 over the vial to afford an off-white solid (0.375 g, 99%). ^{1}H NMR (400 MHz, DMF-d_6) δ 10.14 (s, 1H), 7.75 (*app* dt, *J* = 6.98, 8.59 Hz, 1H), 7.67-7.64 (m, 2H), 7.30 (ddd, *J* = 2.55, 9.26, 11.81 Hz, 1H), 7.21-7.17 (m, 3H), 6.61 (s, 1H), 5.37 (s, 4H), 5.11 (q, *J* = 6.85 Hz, 1H), 2.40 (s, 3H), 2.10 (s, 3H), 1.46 (d, *J* = 6.85 Hz, 3H). ES-HRMS *m/z* 549.0790 (M+H calcd for $C_{25}H_{23}BrF_2N_2O_5$ requires 549.0831).

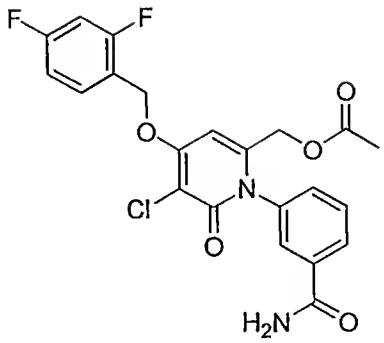
Example 705



2-[(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}phenyl)amino]-1,1-dimethyl-2-oxoethyl acetate

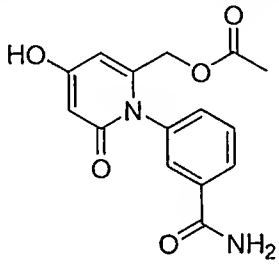
By the method for Example 704 and substituting (S)-(-)-2-acetoxypropionyl chloride with 2-acetoxy-2-methylpropionyl chloride, the title compound was prepared (0.380 g, 98%). ^{1}H NMR (400 MHz, DMF-d_6) δ 9.68 (s, 1H), 7.75 (*app* dt, *J* = 6.72, 8.60 Hz, 1H), 7.71-7.68 (m, 2H), 7.30 (ddd, *J* = 2.55, 9.40, 11.95 Hz, 1H), 7.21-7.15 (m, 3H), 6.61 (s, 1H), 5.37 (s, 4H), 2.41 (s, 3H), 2.04 (s, 3H), 1.59 (s, 6H). ES-HRMS *m/z* 563.1027 (M+H calcd for $C_{26}H_{25}BrF_2N_2O_5$ requires 563.0988).

Example 706



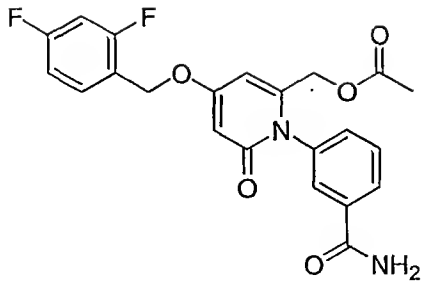
{1-[3-(aminocarbonyl)phenyl]-5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxo-1,6-dihydropyridin-2-yl}methyl acetate

Step 1: Preparation of {1-[3-(aminocarbonyl)phenyl]-4-hydroxy-6-oxo-1,6-dihydropyridin-2-yl}methyl acetate.



3-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-2-oxopropyl acetate (4.00 g, 16.52 mmol) was dissolved in 1,4-dioxane (160 mL) and 3-aminobenzamide (1.73 g, 12.71 mmol) was added. The reaction was heated to reflux for 1 hour then cooled to 70 °C. Methanesulfonic acid (1.22 g, 12.71 mmol) was added and the reaction brought back to reflux for 1 hour. The reaction was cooled to room temperature, concentrated and used as crude product for the next step.

Step 2: Preparation of {1-[3-(aminocarbonyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-oxo-1,6-dihydropyridin-2-yl}methyl acetate.



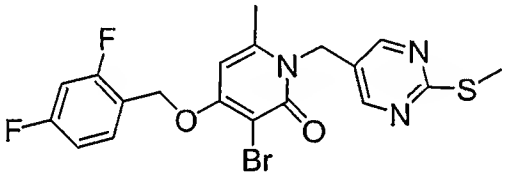
{1-[3-(aminocarbonyl)phenyl]-4-hydroxy-6-oxo-1,6-dihydropyridin-2-yl}methyl acetate (crude from step 1) (3.61 g, 11.94 mmol) was dissolved in *N,N*-dimethylformamide (40 mL). K_2CO_3 (3.80 g, 27.46 mmol) was added followed by 2,4-difluorobenzyl bromide (5.44 g, 26.27 mmol). The reaction mixture was stirred for 48 hours at room temperature. The reaction mixture was then partially concentrated and the residue taken up in dichloromethane/tetrahydrofuran 1:1 and filtered. The filtrate was collected, concentrated and the residue tritrated with dichloromethane to afford a tan solid (1.64 g, 32%). ^{1}H NMR (400 MHz, DMF-d_6) δ 8.19 (br s, 1H), 8.07 (*app* dt, J = 1.35, 7.66 Hz, 1H), 7.91 (*app* t, J = 1.81 Hz, 1H), 7.76 (*app* dt, J = 6.58, 8.59 Hz, 1H) 7.62 (t, J = 7.79 Hz, 1H), 7.55 (ddd, J = 1.21, 2.01, 7.79 Hz, 1H), 7.46 (br s, 1H), 7.34 (ddd, J = 2.55, 9.40, 10.47 Hz, 1H), 7.23-7.18 (m, 1H), 6.26 (d, J = 2.55 Hz, 1H), 6.11 (d, J = 2.69 Hz, 1H), 5.23 (s, 2H), 4.62 (AB q, J_{AB} = 14.97 Hz, 2H), 1.96 (s, 3H). ES-HRMS *m/z* 429.1280 (M+H calcd for $C_{22}H_{18}F_2N_2O_5$ requires 429.1257).

Step 3: Preparation of the title compound .

{1-[3-(aminocarbonyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-oxo-1,6-dihydropyridin-2-yl}methyl acetate (from step 2) (1.02 g, 2.39 mmol) was suspended in dichloromethane (15 mL) and *N*-chlorosuccinimide (0.37 g, 2.75 mmol) was added. Dichloroacetic acid (0.10 ml, 1.22 mmol) was added and the reaction mixture was stirred at 40 °C for 1.5 hours. The

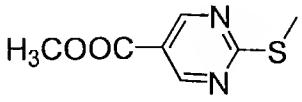
reaction was cooled to room temperature and a precipitate formed. The reaction mixture was diluted with diethyl ether and the precipitate was collected by filtration and washed with diethyl ether (3 x 15 mL) to afford a tan solid (0.940 g, 85%). ^{1}H NMR (400 MHz, DMF-d_6) δ 8.21 (*br* s, 1H), 8.11 (*app* dt, J = 1.48, 7.52 Hz, 1H), 7.95 (*app* t, J = 1.61 Hz, 1H), 7.80 (*app* dt, J = 6.72, 8.59 Hz, 1H) 7.69-7.60 (m, 2H), 7.48 (*br* s, 1H), 7.35 (ddd, J = 2.55, 9.53, 10.61 Hz, 1H), 7.24-7.19 (m, 1H), 6.97 (s, 1H), 5.49 (s, 2H), 4.71 (AB q, J_{AB} = 15.04 Hz, 2H), 1.98 (s, 3H). ES-HRMS *m/z* 463.0883 (M+H calcd for $C_{22}H_{17}ClF_2N_2O_5$ requires 463.0867).

Example 707



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylthio)pyrimidin-5-yl]methyl}pyridin-2(1*H*)-one

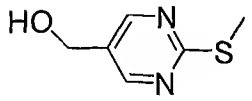
Step 1. Preparation of methyl 2-(methylthio)pyrimidine-5-carboxylate



A solution of the sodium salt of 3,3-dimethoxy-2-methoxycarbonylpropen-1-ol (5.0g, 25 mmol), 2-methyl-2-thiopseudourea sulfate (3.5g, 25 mmol) in anhydrous methanol (25 mL) was refluxed for 3 hours under anhydrous conditions. The reaction mixture was cooled and diluted with ethyl acetate. The reaction mixture was filtered and the residue was washed with ethyl acetate. The filtrate was concentrated and the residue was purified by flash chromatography (silica

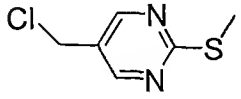
gel) using 25% ethyl acetate in hexane to afford the desired product (3.5g, 75%) as a white powder. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ 9.0 (s, 2H), 3.92 (s, 3H), 2.58 (s, 3H); ES-HRMS *m/z* 185.041 (M+H $C_7H_8N_2O_2S$ requires 185.0379).

Step 2. Preparation of [2-(methylthio)pyrimidin-5-yl]methanol



To a cold suspension of methyl 2-(methylthio)pyrimidine-5-carboxylate (1.74g, 9.4 mmol) in dichloromethane (20 mL, -70° C) was added DIBAL (20.8 mL, 20 mmol) dropwise via an addition funnel. The mixture was stirred under nitrogen at -70° C for 1 hour and then at -50° C for 3 hours. The reaction was diluted with dichloromethane (50 mL) and quenched with a suspension of sodium sulfate decahydrate (10g) in water (50 mL). The slurry was filtered through celite and the filtrate was concentrated. The residue was purified by flash chromatography (silica gel) using 100% ethyl acetate to afford the desired compound (0.7813 g, 39%) as a yellow solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.53 (s, 2H), 4.56 (s, 2H), 2.54 (s, 3H); ES-HRMS *m/z* 157.0409 (M+H $C_6H_8N_2OS$ requires 157.0430).

Step 3. Preparation of 5-(chloromethyl)-2-(methylthio)pyrimidine



To a cold solution of [2-(methylthio)pyrimidin-5-yl]methanol (0.7813g, 5.0 mmol) in anhydrous dichloromethane (10 mL, 0° C) was added triethylamine (0.836 mL, 8.2 mmol) followed by the addition of methanesulfonyl chloride (0.465mL, 6.0 mmol). The reaction mixture stirred at 0° C under a

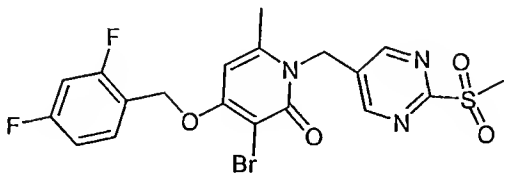
nitrogen atmosphere for 30 minutes then at room temperature for 3.5 hours. The reaction was quenched with sodium bicarbonate (5%, 100 mL)) and extracted with dichloromethane (50 mL). The organic extracts were concentrated and the residue was purified by flash chromatography (silica gel) using 15% ethyl acetate in hexane to afford the desired compound (0.720 g, 82%) as a white solid. ^{1}H-NMR ((CD_3OD, 400 MHz) δ 8.60 (s, 2H), 4.64 (s, 2H), 2.54 (s, 3H); ES-HRMS *m/z* 175.0106 (M+H $C_6H_7N_2ClS$ requires 175.0091).

Step 4. Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylthio)pyrimidin-5-yl]methyl}pyridin-2(1*H*)-one

To a solution of 5-(chloromethyl)-2-(methylthio)pyrimidine (0.62g, 3.56 mmol) in anhdrous DMF (10 mL) was added KBr (0.424, 3.56 mmol). After the suspension stirred at room temperature for 30 minutes, 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (1.05g, 3.19 mmol) was added followed by NaH (0.102g, 4.25 mmol). The reaction mixture stirred at 70° C under a nitrogen atmosphere for 3.5 hours. The solvent was distilled and the residue was washed with water and extracted with ethyl acetate. The organic extracts were concentrated and the residue was purified by reverse phase HPLC using a 10-90% acetonitrile/water (30 minute gradient) at a 70mL/min flow rate to afford the desired TFA salt (0.32 g, 15%) as a white powder. The TFA compound was washed with sodium bicarbonate (5%) and extracted with dichloromethane. The organic extract was concentrated to afford the desired compound (0.295g, 18 %) as a yellow solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.47 (s, 2H), 7.62 (q, 1H, J= 8Hz), 7.03 (m, 2H), 6.51 (s, 1H), 5.31 (s, 2H), 5.29 (s, 2H), 2.52 (s, 3H), 2.47 (s, 2H); ES-HRMS *m/z*

468.0174/470.0156 (M+H $C_{19}H_{16}N_3O_2F_2BrS$ requires 468.0187/470.0168).

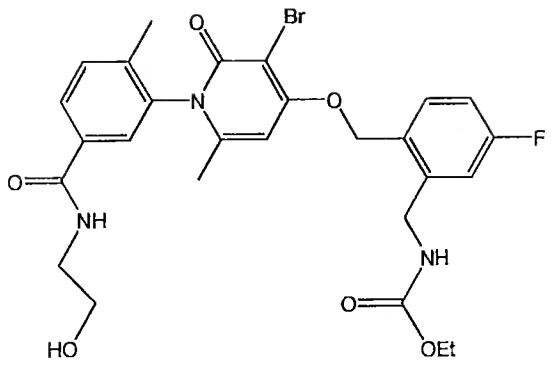
Example 708



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylsulfonyl)pyrimidin-5-yl]methyl}pyridin-2(1*H*)-one

To a solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylthio)pyrimidin-5-yl]methyl}pyridin-2(1H)-one (example 707) (0.26g, 0.55 mmol) in acetonitrile: water (4:1 v/v, 10 mL) was added MMPP (0.549g, 1.1 mmol). The reaction stirred at room temperature for 30 hours. The reaction mixture was diluted with ethyl acetate and filtered. The filtrate was concentrated and the residue was purified by reverse phase HPLC using a 10-90% acetonitrile/water (30 minute gradient) at a 70mL/min flow rate to afford the desired TFA salt of the title copmound (0.13 g, 38%) as a white powder. ^{1}H-NMR ((CD_3OD, 400 MHz) δ 8.86 (s, 2H), 7.62 (q, 1H, J= 8Hz), 7.02 (m, 2H), 6.56 (s, 1H), 5.48 (s, 2H), 5.31 (s, 2H), 3.34 (s, 3H), 2.49 (s, 2H); ES-HRMS *m/z* 500.0109/502.0066 (M+H $C_{19}H_{16}N_3O_4F_2BrS$ requires 500.0086/502.0067).

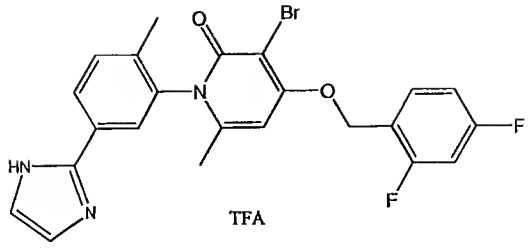
Example 709



Ethyl 2-({[3-bromo-1-(5-{[(2-hydroxyethyl)amino]carbonyl}-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

To a cooled (-10°C) solution of 3-[3-bromo-4-[(2-{[(ethoxycarbonyl)amino]methyl}-4-fluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoic acid (0.25 g, 0.46 mmol) and 4-methylmorpholine (0.06 mL, 0.55mmol) in DMF was added isobutyl chloroformate (0.07 mL, 0.55 mmol). The colorless solution gradually turned dark brown. After 30 min, ethaolamine (0.04 mL, 0.69 mmol) was added and the solution warmed to RT. After 1h, solvent was removed and the crude product was purified by preparatory HPLC. Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (20 mL) and extracted in DCM (3 x 15 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated to a white solid, dried *in vacuo* (0.09 g, 33%). ^1H NMR (CD_3OD/ 400MHz) δ 7.88 (m, 1H), 7.61 (s, 1H), 7.53 (m, 2H), 7.13 (m, 1H), 7.05 (m, 1H), 6.68 (s, 1H), 5.40 (s, 2H), 4.43 (s, 2H), 4.07 (q, 2H, J = 7.2 Hz), 3.68 (t, 2H, J = 5.6 Hz), 3.48 (t, 2H, J = 5.6 Hz), 2.09 (s, 3H), 2.00 (s, 3H), 1.22 (t, 3H , J = 7.2 Hz). ESHRMS *m/z* 590.1266 and 592.1254 (M+H calculated for $C_{27}H_{30}BrFN_3O_6$ requires 590.1297 and 592.1281).

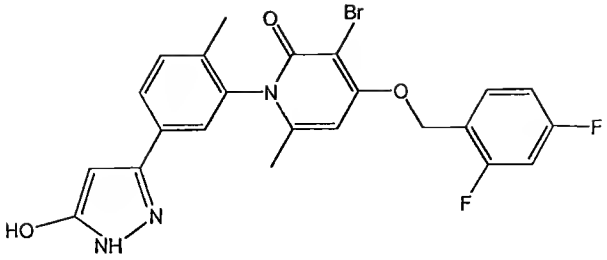
Example 710



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(1H-imidazol-2-yl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one trifluoroacetate

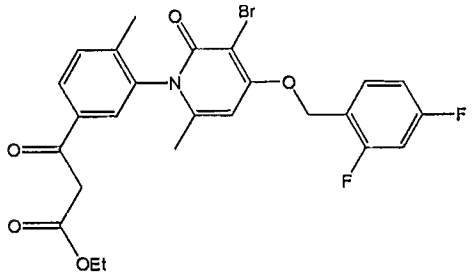
An oven-dried flask was alternately evacuated and flushed with argon. Toluene (2.18 mL) and trimethyl aluminum (1.25 mL, 2.51 mmol) were added sequentially and the solution cooled to -5°C. Ethylene diamine (0.17 mL, 2.51 mmol) was added dropwise. Methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoate (0.75 g, 1.57 mmol) was added portionwise to the cooled solution. The reaction mixture was then refluxed at 110°C for 4h. The solution was cooled and water (0.7 mL), DCM (2.2 mL), and MeOH (2.2 mL) were added. The solution was refluxed for 15 min following this addition and then dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in EtOAc (20 mL), refluxed 15 min, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by preparatory HPLC. The product was isolated by freeze-drying and evaporation of the solvent to give a white solid, dried *in vacuo* (0.30 g, 31%). ^1H NMR (CD_3OD/ 400MHz) δ 7.88 (m, 1H), 7.71 (d, 1H, J = 8.0 Hz), 7.64 (m, 2H), 7.05 (m, 2H), 6.70 (s, 1H), 5.37 (s, 2H), 4.09 (s, 4H), 2.16 (s, 3H), 2.01 (s, 3H). ESHRMS *m/z* 488.0750 and 490.0774 (M+H calculated for $C_{23}H_{21}BrF_2N_3O_2$ requires 488.0780 and 490.0762).

Example 711



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(5-hydroxy-1H-pyrazol-3-yl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one

Step 1: Preparation of ethyl 3-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylphenyl}-3-oxopropanoate.

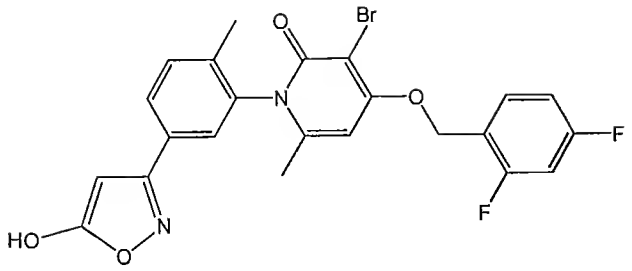


In an oven-dried round bottom flask, 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoic acid (see Example 487) (0.75 g, 1.62 mmol), DCM (2.00 mL), and oxalyl chloride (0.97 mL, 1.94 mmol) were combined under argon. DMF (3-5 drops) was added to aid in dissolution. Stirred at RT overnight. Solvent was removed and the crude acid chloride was coevaporated with DCM (3-5 mL x 3) and dried in vacuo to give an orange solid. In a separate oven-dried flask, in an argon atmosphere, a solution of monoethyl malonate (0.38 mL, 3.23 mmol) in THF (3.00 mL) was cooled to -78°C. Isopropyl magnesium chloride (3.23 mL, 6.46 mmol) was added dropwise. The solution was stirred for 30 min at -78°C. The acid chloride prepared as described above was added dropwise as a solution in THF. The reaction was warmed to RT. After 30 min, the reaction was cooled (0°C) and 10% citric acid (5.0 mL) added. The crude product was extracted in EtOAc, washed with 5% $NaHCO_3$, dried over Na_2SO_4, filtered,

and concentrated to a crude brown oil. Recrystallization from DCM and hexane. Filtered a beige solid, dried *in vacuo* (0.41 g, 47%). ^{1}H NMR (CD_3OD/ 400MHz) δ 8.02 (m, 1H), 7.79 (s, 1H), 7.65 (m, 2H), 7.05 (t, 2H, *J* = 9.2 Hz), 6.66 (s, 1H), 5.36 (s, 2H), 4.16 (q, 2H, *J* = 7.2 Hz), 2.11 (s, 3H), 2.07 (s, 2H), 1.99 (s, 3H), 1.23 (t, 3H, *J* = 7.2 Hz). ESHRMS *m/z* 534.0744 and 536.0746 (M+H calculated for $C_{25}H_{23}BrF_2NO_5$ requires 534.0722 and 536.0706).

Step 2: Preparation of the title compound .
To a mixture of ethyl 3-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylphenyl}-3-oxopropanoate (from Step 1) (0.20 g, 0.37 mmol) in EtOH (5.00 mL) was added hydrazine hydrate (0.01 mL, 0.41 mmol). The reaction mixture was heated at 60°C with a condensere. After 1h, additional hydrazine hydrate (0.01 mL) was added. After 2h, acetic acid (2 drops) was added. At 4h, additional hydrazine was added (0.1 mL). At 5h, the reaction appeared to be complete. Left in fridge overnight. Precipitate filtered, washed with hexane, found to be product, a white solid (0.10 g, 54%). ^{1}H NMR (CD_3OD/ 400MHz) δ 7.66 (m, 2H), 7.45 (m, 2H), 7.05 (t, 2H, *J* = 9.6 Hz), 6.65 (s, 1H), 5.36 (s, 2H), 2.04 (s, 3H), 2.02 (s, 3H). ESHRMS *m/z* 502.0552 and 504.0569 (M+H calculated for $C_{23}H_{19}BrF_2N_3O_3$ requires 502.0572 and 504.0555).

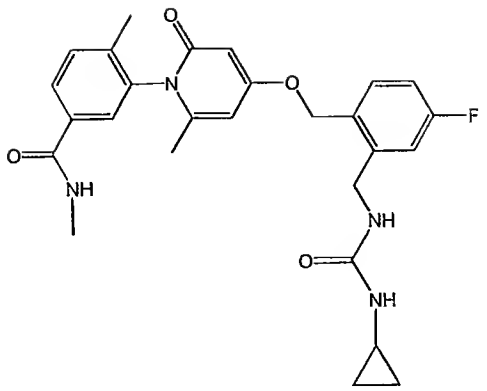
Example 712



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(5-hydroxyisoxazol-3-yl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one

A solution of ethyl 3-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylphenyl}-3-oxopropanoate (0.20 g, 0.37 mmol), triethylamine (0.06 mL, 0.41 mmol), and hydroxylamine hydrochloride (0.03 g, 0.41 mmol) in EtOH (3.00 mL) was heated overnight at 60°C with a condenser. Additional triethylamine (0.06 mL) and hydroxylamine hydrochloride (0.03 g) were added. After 2.5h, the additions of triethylamine and hydroxylamine hydrochloride were repeated. After 1h, the reaction was concentrated and purified by preparatory HPLC. The product was isolated by freeze-drying and evaporation of the solvent to give a white solid. Dissolved solid in DCM. Upon addition of 5% $NaHCO_3$, solution became a milky emulsion. Added additional DCM and some brine. Organic extracts were dried over Na_2SO_4, filtered, and concentrated to a pink solid, dried *in vacuo* (120 mg, 64%). ^1H NMR (CD_3OD/ 400MHz) δ 7.66 (m, 2H), 7.44 (m, 2H), 7.04 (t, 2H, *J* = 8.8 Hz), 6.64 (s, 1H), 5.36 (s, 2H), 2.04 (s, 3H), 2.01 (s, 3H). ESHRMS m/z 503.0415 and 505.0402 (M+H calculated for $C_{23}H_{18}BrF_2N_2O_4$ requires 503.0413 and 505.0395).

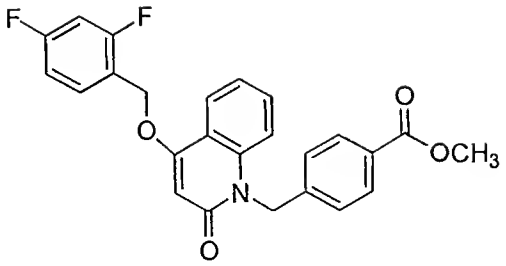
Example 713



3-[4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2*H*)-yl]-N,4-dimethylbenzamide

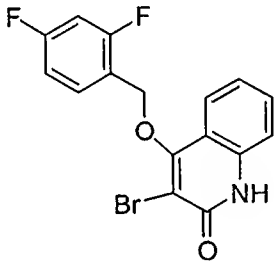
To a cooled (-15°C) solution of 3-[4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoic acid (see Example 651) (0.30 g, 0.63 mmol) and isobutyl chloroformate (0.10 mL, 0.75 mmol) in DMF (3.00 mL) was added 4-methylmorpholine (0.08mL, 0.75 mmol). The solution instantly turned yellow and was dark brown within minutes. After 20 min, methylamine (0.47 mL of 2.0M solution in THF, 0.94 mmol) was added. The reaction was carried out at RT. After 2.5h, a catalytic amount of DMAP and additional methylamine (0.47 mL, 0.94 mmol) were added. After an additional 2.5h, the reaction was concentrated to a dark red oil. The crude product was purified by preparatory HPLC. Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (20 mL) and extracted in DCM (3 x 15 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated to an off-white solid, dried *in vacuo* (0.06 g, 19%). ^1H NMR (CD_3OD/ 400MHz) δ 7.85 (m, 1H), 7.58 (s, 1H), 7.48 (m, 2H), 7.14 (m, 1H), 7.02 (m, 1H), 6.23 (s, 1H), 6.09 (s, 1H), 5.20 (s, 2H), 4.45 (s, 2H), 2.90 (s, 3H), 2.49 (m, 1H), 2.11 (s, 3H), 1.91 (s, 3H), 0.71 (m, 2H), 0.48 (m, 2H). ESHRMS *m/z* 493.2260 (M+H calculated for $C_{27}H_{30}N_4O_4F$ requires 493.2246).

Example 714



Methyl 4-{[4-[(2,4-difluorobenzyl)oxy]-2-oxoquinolin-1(2*H*)-yl]methyl}benzoate

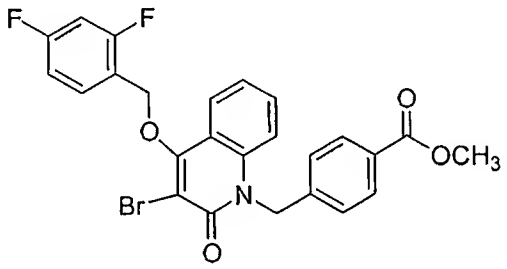
Step 1: Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]quinolin-2(1*H*)-one .



To a room temperature solution of 4-hydroxy-1,2-dihydroquinolin-2-one (500 mg, 3.10 mmol) in CH_2Cl_2 (10.0 mL) was added portion-wise solid *N*-bromosuccinimide (551.5 mg, 3.10 mmol). The reaction was stirred vigorously for 1.0 h, followed by the sequential addition of K_2CO_3 (540 mg, 3.90 mmol), DMF (4.0 mL), and 2,4 difluorobenzyl bromide (0.430 mL, 3.30 mmol). The resulting suspension was stirred for 4.5 hours until complete formation of desired product was seen by LCMS analysis. The reaction was then diluted with ethyl acetate (400 mL) and brine washed (3 X 200 mL). The resulting organic extract was Na_2SO_4 dried, filtered, and concentrated *in vacuo* to a residue that was subjected to SiO_2 chromatography with ethyl acetate/hexanes/methanol (60:35:5) to furnish a

solid (529 mg, 47 %). ^{1}H NMR (300 MHz, d_6-DMSO) δ 12.23 (s, 1H), 7.68 (*app* q, *J* = 7.5 Hz, 1H), 7.64 (*app* q, *J* = 8.5 Hz, 1H), 7.54 (*app* q, *J* = 8.3 Hz, 1H), 7.38-7.27 (m, 2H), 7.20 (*app* t, *J* = 7.4 Hz, 1H), 7.13 (*app* dt, *J* = 8.4, 2.6 Hz, 1H), 5.25 (s, 2H); LC/MS C-18 column, t_r = 2.64 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 366 (M+H). ES-HRMS *m/z* 365.9967 (M+H calcd for $C_{16}H_{11}BrF_2NO_2$ requires 365.9936).

Step 2: Preparation of methyl 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxoquinolin-1(2*H*)- yl]methyl}benzoate .

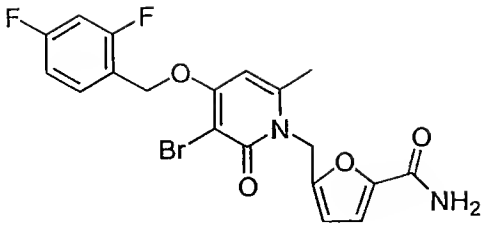


To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]quinolin-2(1*H*)-one (400 mg, 1.09 mmol) in THF (4.5 mL) was added portion-wise solid sodium hydride (95 % oil-free, 60.0 mg, 2.49 mmol). The reaction was vigorously stirred for 30 minutes followed by addition of methyl-4-(bromomethyl)-benzoate (400 mg, 1.75 mmol). This resulting suspension was then heated to 60 °C for 12.0 hours. The resulting solution was then treated with saturated aqueous ammonium chloride (400 mL) and extracted with ethyl acetate (3 X 300 mL). The resulting organic extracts were Na_2SO_4 dried, filtered, and concentrated *in vacuo* to a residue that was subjected to SiO_2 chromatography with ethyl acetate/hexanes (60:40) to furnish a solid (396 mg, 71 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (*app* d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.60 (*app* q, *J* = 8.4 Hz, 1H), 7.49-7.42 (m, 1H), 7.30-7.15 (m, 4H), 6.94 (*app* t, *J* = 6.3 Hz, 1H), 6.88 (*app* t, *J* =

9.4 Hz, 1H), 5.64 (s, 2H), 5.33 (s, 2H), 3.88 (s, 3H); LC/MS C-18 column, t_r = 3.46 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 514 (M+H). ES-HRMS *m/z* 514.0451 (M+H calcd for $C_{25}H_{19}BrF_2NO_4$ requires 514.0460).

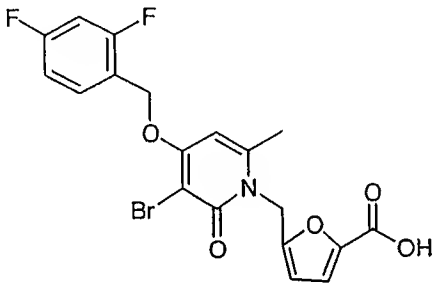
Step 3: Preparation of the title compound . In a 25 mL round bottom flask was added, at room temperature, a solution of methyl 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxoquinolin-1(2H)- yl]methyl}benzoate (step 2) (120 mg, 0.233 mmol) in MeOH (3.0 mL). Next, a combination of Pd on carbon (10 % Pd, weight by weight 50 % water, 100 mg, 0.047 mmol) and $Pd(OAc)_2$ (15 mg, 0.067 mmol) was added to the reaction vessel that purged with argon and then fitted with a septum. The vessel was then equipped with a 2.0 L hydrogen balloon (*c.a.* 20 psi). The resulting suspension was allowed to stir of 12.0 hours and was then directly applied to SiO_2 chromatography using ethyl acetate/ hexanes (3:7) to furnish the desired title compound as a solid (52 mg, 51 %). ^1H NMR (300 MHz, $CDCl_3$) δ 8.05-7.98 (m, 3H), 7.55 (*app* q, *J* = 8.3 Hz, 1H), 7.48 (app t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.0 Hz 2H), 7.19 (*app* q, *J* = 8.5, 2H), 7.05-6.90 (m, 2H), 6.28 (s, 1H), 5.60 (s, 2H), 5.26 (s, 2H), 3.91 (s, 3H); LC/MS C-18 column, t_r = 3.71 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 436 (M+H). ES-HRMS *m/z* 436.1371 (M+H calcd for $C_{25}H_{20}BrF_2NO_4$ requires 436.1355).

Example 715



5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-2-furamide

Step 1: Preparation of 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-2-furoic acid .

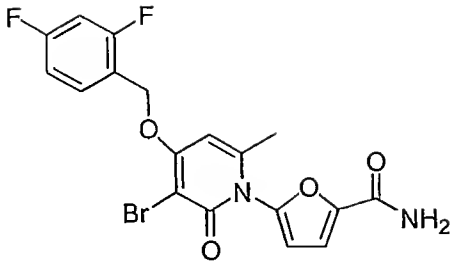


To a room temperature solution of methyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)- yl]methyl}-2-furoate (Example 660) (608 g, 1.30 mmol) in THF (8.0 mL) was added dropwise an aqueous solution of sodium hydroxide (3.0 M, 0.50 mL, 1.50 mmol). The reaction was then heated to 60 °C for 12.0 hours. The resulting suspension was then diluted with 500 mL of ethyl acetate and neutralized with an aqueous solution of hydrochloric acid (1.0 N, 1.5 mL, 10 mmol). The resulting biphasic solution was then concentrated *in vacuo* to a volume of 50 mL. At this time a white solid began to form and the resulting solid suspension was allowed to sit until precipitation appeared to stop (approximately 1.0 hour). The precipitate was collected and dried *in vacuo* (1.0 mm Hg) to furnish the solid acid as an intermediate (500 mg, 85 %). ^{1}H NMR (300 MHz, d_4-MeOH) δ 7.64 (*app* q, *J* = 8.3 Hz, 1H), 7.18 (d, *J* = 3.4 Hz, 1H), 7.10-7.02 (m, 2H), 6.54 (s, 1H), 6.50 (d, *J* =

3.5 Hz, 1H), 5.42 (s, 2H), 5.37 (s, 2H), 2.64 (s, 3H); LC/MS C-18 column, t_r = 2.38 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 454 (M+H). ES-HRMS *m/z* 454.0070 (M+H calcd for $C_{19}H_{15}BrF_2NO_5$ requires 454.0096).

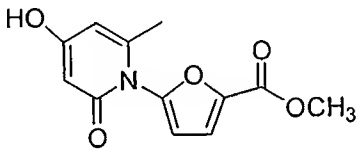
Step 2: Preparation of the title compound. To a room temperature suspension of 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-2-furoic acid (500 mg, 1.10 mmol) in THF (6.0 mL) was added 2-chloro-4,6 dimethoxy-1,3,5 triazine (307 mg, 1.75 mmol) and N-methyl morpholine (NMM, 184 mg, 1.82 mmol) sequentially. The resulting solution was matured for 2 hours and then a saturated aqueous solution of ammonium hydroxide (0.70 mL) was added. The resulting suspension was allowed to continue for 1 additional hour. The reaction mixture was diluted with 400 mL of brine and extracted with ethyl acetate (3 X 400 mL). The organic extracts were separated, Na_2SO_4 dried, and concentrated *in vacuo* and the resulting residue was subjected to SiO_2 chromatography with ethyl acetate/hexanes/methanol (57:38:5) to provide the title compound (370 g, 74 %). ^1H NMR (300 MHz, d_4-MeOH) δ 7.64 (*app* q, *J* = 8.1 Hz, 1H), 7.10-7.00 (m, 3H), 6.53 (s, 1H), 6.52 (d, *J* = 3.4 Hz, 1H), 5.43 (s, 2H), 5.32 (s, 2H), 2.61 (s, 3H); LC/MS C-18 column, t_r = 2.15 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 453 (M+H). ES-HRMS *m/z* 453.0249 (M+H calcd for $C_{19}H_{16}BrF_2N_2O_4$ requires 453.0256).

Example 716



5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-furamide

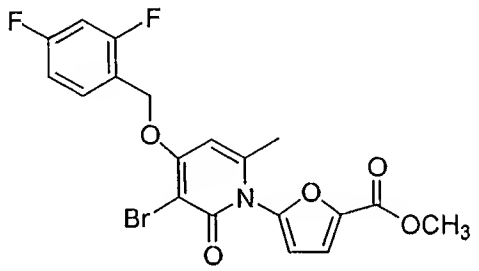
Step 1: Preparation of methyl 5-(4-hydroxy-6-methyl-2-oxopyridin-1(2*H*)-yl)-2-furoate .



To a room temperature solution of methyl-2-amino-5-furoate (4.85 g, 34.4 mmol) in 1,4 dioxane (28.0 mL) was added 5-(1-hydroxy-3-oxobutylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (8.16 g, 44.3 mmol). The reaction was stirred vigorously and heated quickly (within 8 minutes) to an internal temperature of 98 °C. Upon reaching temperature, the reaction was maintained for 1.0 hour. At this time, the reaction was cooled to room temperature rapidly using an ice-bath and methane sulfonic acid (3.30 g, 34.4 mmol) was added. The reaction mixture was once again brought to an internal temperature of approximately 100 °C. After 1.0 hour the reaction was diluted with 10 mL of toluene and allowed to cool to room temperature on its own accord. A solid formed after 3.0 hours that was collected and subsequently recrystallized from methanol/ ethyl acetate (1:1). The developing crystals were allowed to form and stand for 12.0 hours prior to collection to furnish the desired product as a solid (3.78 g, 44 %). ^{1}H NMR (400 MHz, d_7-DMF) δ 11.34 (s, 1H), 7.43 (*app* d, *J* = 3.6 Hz, 1H), 6.79 (*app*

d, J = 3.6 Hz, 1H), 6.01 (s, 1H), 5.63 (d, J = 2.0 Hz, 1H), 3.87 (s, 3H), 2.02 (s, 3H); LC/MS C-18 column, t_r = 1.47 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 250 (M+H). ES-HRMS m/z 250.0696 (M+H calcd for $C_{12}H_{12}NO_5$ requires 250.0710).

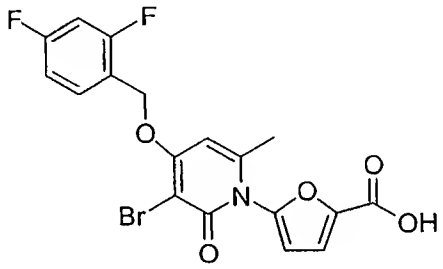
Step 2: Preparation of methyl 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-furoate.



To a room temperature solution of methyl 5-(4-hydroxy-6-methyl-2-oxopyridin-1(2*H*)-yl)-2-furoate (step 1) (3.19 g, 12.8 mmol) in DMF (14 mL) was added portion-wise solid *N*-bromosuccinimide (2.29 g, 12.9 mmol). The reaction was stirred vigorously for 1.0 h, followed by the sequential addition of K_2CO_3 (1.88 g, 13.6 mmol), DMF (4.0 mL), and 2,4 difluorobenzyl bromide (2.00 mL, 15.55 mmol). The resulting suspension was stirred for 9.0 hours until complete formation of desired product was seen by LCMS analysis. The reaction was then diluted with saturated brine (300 mL) and extracted with ethyl acetate (3 X 300 mL). The resulting organic extracts were Na_2SO_4 dried, filtered, and concentrated *in vacuo* to a residue that was subjected to SiO_2 chromatography with a gradient elution using ethyl acetate/hexanes (40:60 to 60:40) to furnish a solid (3.20 mg, 55 %). ^{1}H NMR (400 MHz, d_7-DMF) δ 7.78 (*app* q, J = 8.6 Hz, 1H), 7.48 (*app* d, J = 3.6 Hz, 1H), 7.33 (*app* dt, J = 10.0, 2.4 Hz, 1H), 7.21 (*app* dt, J = 8.5, 1.8 Hz, 1H), 6.92 (d, J = 3.6 Hz, 1H), 6.81 (s, 1H), 5.47 (s,

2H), 3.88 (s, 3H), 2.15 (s, 3H); LC/MS C-18 column, t_r = 3.11 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 454 (M+H). ES-HRMS *m/z* 454.0117 (M+H calcd for $C_{19}H_{15}BrF_2N_2O_5$ requires 454.0096).

Step 3: 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-furoic acid .



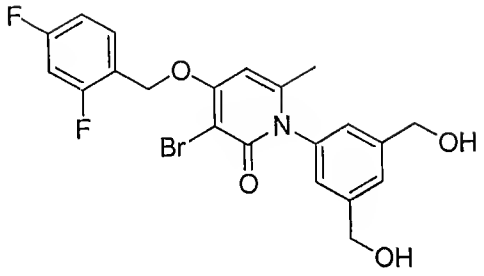
To a room temperature solution of methyl 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-furoate (step 2) (3.00 g, 6.61 mmol) in THF (20 mL) was added dropwise an aqueous solution of sodium hydroxide (3.0 M, 4.00 mL, 12.0 mmol). The reaction was then heated to 60 °C for 12.0 hours. The resulting suspension was then diluted with 800 mL of ethyl acetate and neutralized with an aqueous solution of hydrochloric acid (3.0 N, 4.0 mL, 12 mmol). The resulting biphasic solution was then concentrated *in vacuo* to a volume of 90 mL. At this time a white solid began to form and the resulting solid suspension was allowed to sit until precipitation appeared to stop (approximately 1.0 hour). The precipitate was collected and dried *in vacuo* (1.0 mm Hg) to furnish the solid acid as an intermediate (2.27 g, 78 %). ^{1}H NMR (400 MHz, d_7-DMF) δ 7.79 (*app* q, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 9.2 Hz, 1H), 7.20 (*app* t, *J* = 7.4 Hz, 1H), 6.88 (*app* d, *J* = 2.5 Hz, 1H), 6.74 (s, 1H), 6.51 (d, *J* = 2.5 Hz, 1H), 5.44 (s, 2H), 2.10 (s, 3H); LC/MS C-18 column, t_r = 2.77 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with

detection 254 nm, at 50°C). ES-MS *m/z* 440 (M+H). ES-HRMS *m/z* 439.9959 (M+H calcd for $C_{18}H_{13}BrF_2NO_5$ requires 439.9940).

Step 4: Preparation of the title compound.

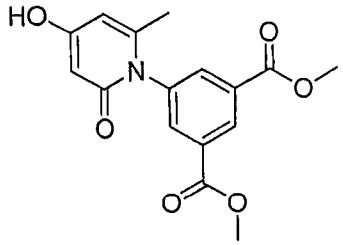
To a room temperature suspension of 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-furoic acid (1.00 g, 2.27 mmol) in THF (8.0 mL) was added 2-chloro-4,6 dimethoxy-1,3,5 triazine (610 mg, 3.47 mmol) and N-methyl morpholine (NMM, 368 mg, 3.62 mmol) sequentially. The resulting solution was matured for 2 hours and then a saturated aqueous solution of ammonium hydroxide (1.5 mL) was added. The resulting suspension was allowed to continue for 1 additional hour. The reaction mixture was diluted with 800 mL of brine and extracted with ethyl acetate (3 X 600 mL). The organic extracts were separated, Na_2SO_4 dried, and concentrated *in vacuo* and the resulting residue was subjected to SiO_2 chromatography with ethyl acetate/hexanes/methanol (57:38:5) to provide the title compound (710 mg, 71 %). ^{1}H NMR (400 MHz, d_7-DMF) δ 8.07 (s, 1H), 7.79 (*app* q, *J* = 8.6 Hz, 1H), 7.50 (*br* s, 1H), 7.32 (*app* dt, *J* = 10.1, 2.2 Hz, 1H), 7.30 (*app* dd, *J* = 8.0, 3.3 Hz, 1H), 7.20 (*app* dt, *J* = 8.6, 2.0 Hz, 1H), 6.81 (s, 1H), 6.79 (d, *J* = 3.4 Hz, 1H), 5.47 (s, 2H), 2.14 (s, 3H); LC/MS C-18 column, t_r = 2.60 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 439 (M+H). ES-HRMS *m/z* 439.0088 (M+H calcd for $C_{18}H_{14}BrF_2N_2O_4$ requires 439.0010).

Example 717



1-[3,5-bis(hydroxymethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

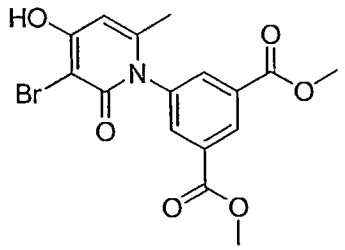
Step 1: Preparation of dimethyl 5-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)isophthalate



Dimethyl 5-aminoisophthalate (24.45 g, 117 mmol) was dissolved in 500 ml toluene and heated to reflux. 5-(1-hydroxy-3-oxobutylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (40.0 g, 175.3 mmol) was added and refluxed for 15 minutes. The reaction was evaporated. 500 ml of acetonitrile and p-toluenesulphonic acid (22.25 g, 117 mmol) was added and refluxed for 1 hour. The reaction was allowed to cool to room temperature and stand over night. The resulting precipitate was filtered, washed three times with 250 ml water and 250 ml acetonitrile and dried *in vacuo* to give a tan solid (18.85 g, 51% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.70 (br s, 1H), 8.47 (t, J = 1.54 Hz, 1H), 7.99 (d, J = 1.47 Hz, 2H), 5.90 (d, J = 1.61 Hz, 1H), 5.55 (d, J = 2.42 Hz, 1H), 3.87 (s, 6H), 1.82 (s, 3H); LC/MS, t_r = 1.79 minutes (5 to 95% acetonitrile/water

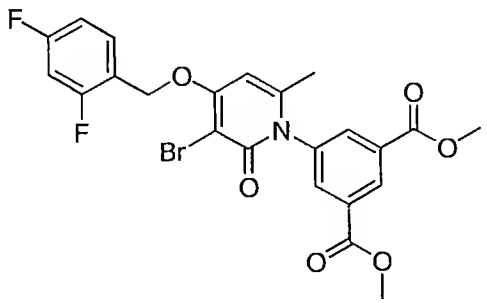
over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 318 (M+H). ES-HRMS *m/z* 318.0994 (M+H calcd for $C_{16}H_{16}NO_6$ requires 318.0972).

Step 2: Preparation of dimethyl 5-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)isophthalate



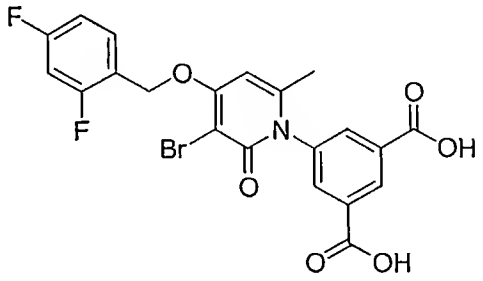
Dimethyl 5-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)isophthalate (from Step 1) (18.0 g, 56.7 mmol) was stirred at room temperature with N-Bromosuccinimide (10.6 g, 59.6 mmol) in 35 ml of *N,N*-dimethylformamide and 180 ml of methylene chloride. After stirring for 1 hour, a white precipitate had formed. The precipitate was filtered, washed with acetonitrile and dried *in vacuo* to give a white solid (11.55 g, 51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.49 (br s, 1H), 8.49 (t, *J* = 1.24 Hz, 1H), 8.06 (d, *J* = 1.47 Hz, 2H), 6.07 (s, 1H), 3.88 (s, 6H), 1.82 (s, 3H); LC/MS, t_r = 1.81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 396 (M+H). ES-HRMS *m/z* 396.0102 (M+H calcd for $C_{16}H_{15}BrNO_6$ requires 396.0077).

Step 3: Preparation of dimethyl 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalate .



Dimethyl 5-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)isophthalate (from Step 2) (11.3 g, 28.5 mmol) was stirred briskly with 2,4-difluorobenzylbromide (3.66 ml, 28.5 mmol) and K_2CO_3 (5.91 g, 42.8 mmol) in 50 ml of *N,N*-dimethylformamide at room temperature for 3 hours. The reaction was then poured into 1L of cold water and the resulting precipitate was filtered, washed with water and diethyl ether, and dried *in vacuo* to yield a white solid (13.8 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (t, *J* = 1.60 Hz, 1H), 8.12, (d, *J* = 1.60 Hz, 2H), 7.67 (*app* q, *J* = 7.92 Hz, 1H), 7.34 (*app* dt, *J* = 9.94, 2.19 Hz, 1H), 7.17 (dt, *J* = 8.53, 2.11 Hz, 1H), 6.68 (s, 1H), 5.33 (s, 2H), 3.88 (s, 6H), 1.93 (s, 3H); LC/MS, t_r = 2.77 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 522 (M+H). ES-HR/MS *m/z* 522.0335 (M+H calcd for $C_{23}H_{19}BrF_2NO_6$ requires 522.0358).

Step 4: Preparation of 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalic acid .

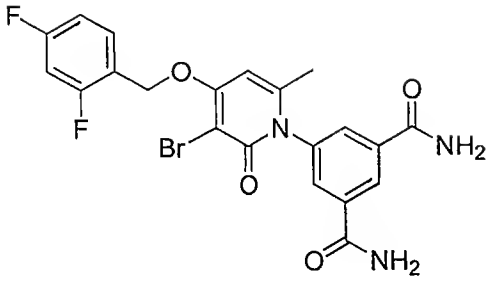


Dimethyl 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalate (from Step 3) (5.0 g, 9.57 mmol) was stirred at room temperature with 2.5 N NaOH (15.3 ml, 38.3 mmol) in 30 ml of 5:1 THF/water for 1 hour. The reaction was then acidified with 1 N HCl and the resulting precipitate was filtered, washed with water, and dried *in vacuo* to yield a white solid (4.48 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.50 (br s, 2H), 8.51 (t, *J* = 1.41 Hz, 1H), 8.02,

(d, *J* = 1.48 Hz, 2H), 7.67 (*app* q, *J* = 7.88 Hz, 1H), 7.32 (dt, *J* = 9.94, 2.19 Hz, 1H), 7.16 (dt, *J* = 8.52, 1.99 Hz, 1H), 6.68 (s, 1H), 5.32 (s, 2H), 1.94 (s, 3H); LC/MS, t_r = 2.27 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 494 (M+H). ES-HRMS *m/z* 494.0054 (M+H calcd for $C_{21}H_{15}BrF_2NO_6$ requires 494.0045).

Step 5: Preparation of the title compound . 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalic acid (from Step 4 above) (500 mg, 1.01 mmol) was added to a solution of 1M borane-dimethylsulfide complex in tetrahydrofuran (9.0 ml, 9.00 mmol) in 2.5 ml tetrahydrofuran at 0°C. The reaction was allowed to warm to room temperature while stirring. After stirring overnight, more 1M borane-dimethylsulfide complex in tetrahydrofuran (0.60 ml, 0.60 mmol) was added and stirring at room temperature. After 4 hours, ice chips were added to quench the reaction. The reaction was extracted 2 times with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated. The resulting solid was washed with acetonitrile and diethyl ether and dried *in vacuo* to give a white solid (281 mg, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (*app* q, *J* = 7.92 Hz, 1H), 7.35 (s, 1H), 7.33 (dt, *J* = 9.40, 2.24 Hz, 1H), 7.16 (dt, *J* = 8.52, 1.88 Hz, 1H), 6.99 (s, 2H), 6.62 (s, 1H), 5.31 (s, 2H), 5.27 (br s, 2H), 4.51 (s, 4H), 1.93 (s, 3H); LC/MS, t_r = 2.19 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 466 (M+H). ES-HRMS *m/z* 466.0454 (M+H calcd for $C_{21}H_{19}BrF_2NO_4$ requires 466.0460).

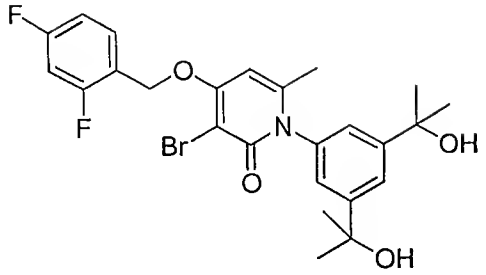
Example 718



5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalamide

5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalic acid (Example 717, step 4) (500 mg, 1.01 mmol) was dissolved in 4 ml of tetrahydrofuran. 0.5M ammonia in 1,4-dioxane (12.12 ml, 6.06 mmol) was added, followed, in order, by EDCI (494 mg, 2.53 mmol), 1-hydroxybenzotriazole (342 mg, 2.53 mmol) and triethylamine (563 μl, 4.04 mmol). The reaction was stirred at room temperature overnight. The reaction evaporated and water was used to triturate the product. The resulting solid was filtered and washed with water, acetonitrile, ethyl acetate and diethyl ether, and dried *in vacuo* to give a white solid (202 mg, 41%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.08 (br s, 2H), 7.86, (d, J = 1.34 Hz, 2H), 7.67 (*app* q, J = 7.92 Hz, 1H), 7.55 (br s, 2H), 7.33 (dt, J = 9.94, 2.18 Hz, 1H), 7.17 (dt, J = 8.59, 1.92 Hz, 1H), 6.70 (s, 1H), 5.34 (s, 2H), 1.96 (s, 3H); LC/MS, t_r = 2.10 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 492 (M+H). ES-HRMS m/z 492.0381 (M+H calcd for $C_{21}H_{17}BrF_2N_3O_4$ requires 492.0365).

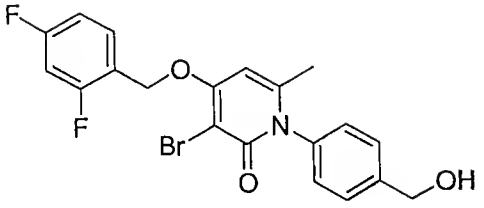
Example 719



1-[3,5-bis(1-hydroxy-1-methylethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Dimethyl 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalate (Example 717, step 3) (500 mg, 0.96 mmol) was added dro pwise to a solution of 3M MeMgBr in diethyl ether (1.6 ml, 4.79 mmol) in 15 ml of tetrahydrofuran at -5°C and stirred at -5°C. The reaction turned red. After 2.5 hours, the reaction was quenched with a saturated NH_4Cl solution and extracted 2 times with ethyl acetate. The combined organic layers were washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated. The resulting solid was washed with diethyl ether and dried *in vacuo* to give a white solid (329 mg, 66%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.69 - 7.63 (m, 2H), 7.33 (dt, J = 9.87, 2.41 Hz, 1H), 7.16 (dt, J = 8.46, 1.75 Hz, 1H), 7.07 (d, J = 1.48 Hz, 2H), 6.61 (s, 1H), 5.32 (s, 2H), 5.06 (s, 2H), 1.89 (s, 3H), 1.41 (s, 12H); LC/MS, t_r = 2.45 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 522 (M+H). ES-HRMS *m/z* 522.1098 (M+H calcd for $C_{25}H_{27}BrF_2NO_4$ requires 522.1086).

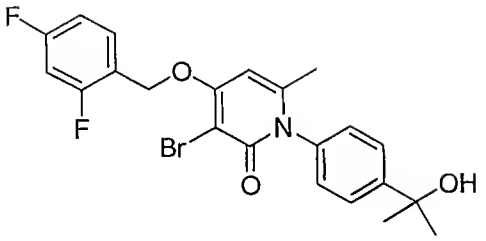
Example 720



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoic acid (Example 203) (500 mg, 1.11 mmol) was added to a solution of 2M borane-dimethylsulfide complex in tetrahydrofuran (3.33 ml, 6.66 mmol) in 2.5 ml tetrahydrofuran at 0°C. The reaction was allowed to warm to room temperature while stirring. After 2.5 hours, ice chips were added to quench the reaction. The resulting precipitate was filtered, washed with diethyl ether and dried *in vacuo* to give a white solid (160 mg, 33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (*app* q, J = 7.88 Hz, 1H), 7.42 (d, J = 8.19 Hz, 2H), 7.33 (dt, J = 9.87, 2.06 Hz, 1H), 7.19 - 7.14 (m, 3H), 6.62 (s, 1H), 5.31 (s, 2H), 5.30 (s, 1H), 4.54 (d, J = 5.24, 2H), 1.92 (s, 3H); LC/MS, t_r = 2.36 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 436 (M+H). ES-HRMS *m/z* 436.0374 (M+H calcd for $C_{20}H_{17}BrF_2NO_3$ requires 436.0354).

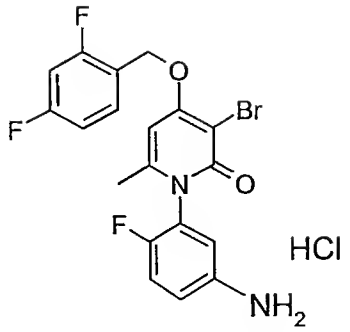
Example 721



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(1-hydroxy-1-methylethyl)phenyl]-6-methylpyridin-2(1H)-one

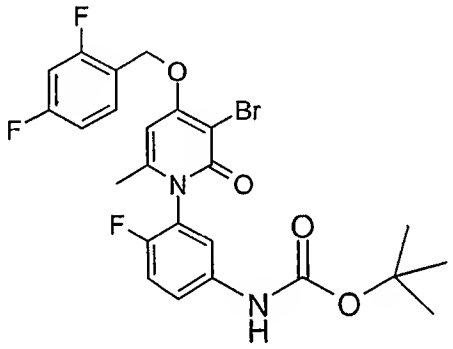
Methyl-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (Example 202) (500 mg, 1.08 mmol) was added dropwise to a solution of 3M MeMgBr in diethyl ether (0.90 ml, 2.69 mmol) in 15 ml of tetrahydrofuran at -5°C and stirred at -5°C. After 2.75 hours, more 3M MeMgBr in diethyl ether (0.45 ml, 1.35 mmol) was added and stirred at -5°C. After 4 hours, the reaction was quenched with a saturated NH_4Cl solution and extracted 2 times with ethyl acetate. The combined organic layers were washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated. The resulting solid was washed with diethyl ether and dried *in vacuo* to give a white solid (268 mg, 53%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.66 (*app* q, J = 7.92 Hz, 1H), 7.57 (d, J = 8.46 Hz, 2H), 7.33 (dt, J = 9.87, 2.11 Hz, 1H), 7.16 (dt, J = 8.59, 2.24 Hz, 1H), 7.14 (d, J = 8.63 Hz, 2H), 6.62 (s, 1H), 5.31 (s, 2H), 5.12 (s, 1H), 1.91 (s, 3H), 1.44 (s, 6H); LC/MS, t_r = 2.54 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 464 (M+H). ES-HRMS *m/z* 464.0604 (M+H calcd for $C_{22}H_{21}BrF_2NO_3$ requires 464.0667).

Example 722



1-(5-amino-2-fluorophenyl)-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride

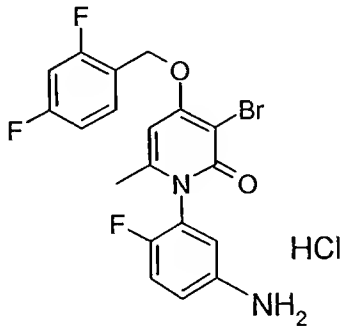
Step 1 Preparation of tert-butyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenylcarbamate



A solution of the compound of Example 519 (4.3 g, 9.2 mmol) in *tert*-butanol (50 mL) was flushed with nitrogen. Diphenyl phosphoryl azide (2 mL, 9.2 mmol) and triethyl amine (1.3 mL, 9.2 mmol) were added. After heating at 90 C for 20 h, the reaction mixture was concentrated *in vacuo*. The residue was diluted with methylene chloride and was washed sequentially with aqueous ammonium chloride and aqueous $NaHCO_3$. The organic layer was concentrated *in vacuo*; the resulting solids were suspended in acetonitrile and filtered to give the title compound (2.9 g, 58%). ^1H NMR (400 MHz, CD_3OD) δ 7.64 (q, J = 7.2 and 14.4 Hz, 1H), 7.49 (m, 1H), 7.43 (m, 1H), 7.24 (t, J = 9.6 Hz, 1H), 7.04 (t, J = 8.4 Hz, 2H), 6.62 (s, 1H), 5.35 (s, 2H), 2.09 (s, 3H), 1.49 (s, 9H) ppm. ^{19} F NMR (300 MHz,

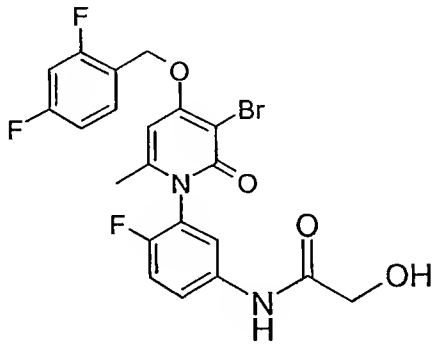
CD_3OD) δ -111.53 (1F), -115.93 (1 F), -132.58 ppm. ES-HRMS *m/z* 540.0822 (M+H calcd for $C_{24}H_{23}BrF_3N_2O_4$ requires 540.0820).

Step 2 Preparation of 1-(5-amino-2-fluorophenyl)-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride



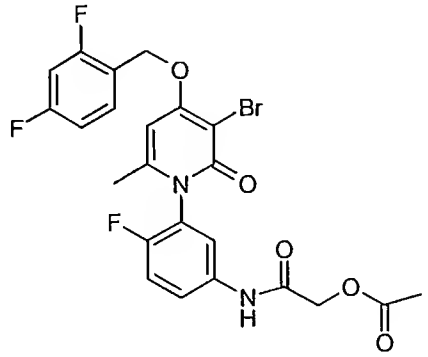
The product of Step 1, (2.9 g, 5.3 mmol) was dissolved in tetrahydrofuran (75 mL) and 6N HCl (10 mL). The reaction mixture was heated at 60 C for 18h and was concentrated in vacuo to give the final product (1.89 g, 75%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (q, *J* = 8.4 and 15.2 Hz, 1H), 7.56 (m, 2H), 7.46 (m, 1H), 7.05 (m, 2H), 6.69 (s, 1H), 5.37 (s, 2H), 2.10 (s, 3H) ppm. ^{19} F NMR (400 MHz, CD_3OD) δ -111.37 (1F), -115.86 (1 F), -123.16 ppm. ES-HRMS *m/z* 440.0334 (M+H calcd for $C_{19}H_{15}BrF_3N_2O_2$ requires 440.0295).

Example 723



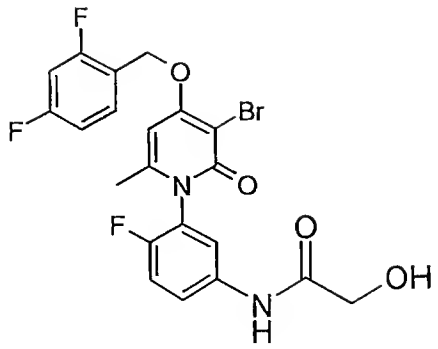
N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenyl}-2-hydroxyacetamide

Step 1 Preparation of 2-({3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenyl}amino)-2-oxoethyl acetate



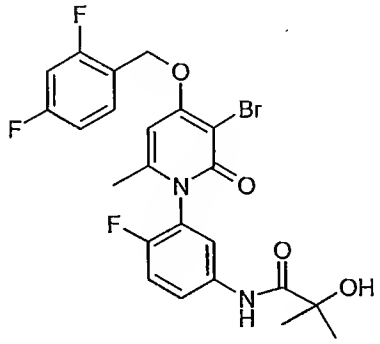
A solution of the compound of Example 722 (0.5 g, 1.05 mmol) in tetrahydrofuran (20 mL) was treated with triethyl amine (0.3 mL, 2.1 mmol) and acetoxy acetylchloride (0.12 mL, 1.15 mmol). After stirring at room temperature for 2h, the reaction was complete. The reaction mixture was poured into saturated aqueous ammonium chloride. The solids were filtered off and were washed with water and diethyl ether. Title product was isolated as a white solid (0.32 g, 58%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.65 (m, 3H), 7.32 (t, J = 8.4 Hz, 1H), 7.04 (t, J = 8.4 Hz, 2H), 6.64 (s, 1H), 5.35 (s, 2H), 4.68 (s, 2H), 2.15 (s, 3H), 2.10 (s, 3H) ppm. ^{19} F NMR (400 MHz, CD_3OD) δ -111.56 (1F), -115.99 (1 F), -129.48 (1F) ppm. LC/MS, t_r = 5.35 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 540 (M+H).

Step 2 Preparation of N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenyl}-2-hydroxyacetamide



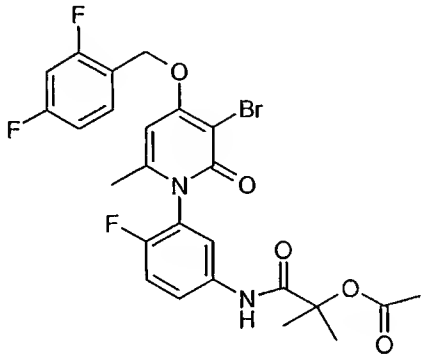
The product of Step 1, (0.1 g, 0.18 mmol) was suspended in tetrahydrofuran (10 mL), methanol (2 mL), and 2.5 N NaOH (1 mL). After stirring at room temperature for 1 hour, the reaction was complete and the organics were removed *in vacuo*. The aqueous layer was acidified to pH 1 with 6N HCl, the solids were suspended in water, filtered, and washed with diethyl ether. The title compound was obtained as a white powder (56.2 mg, 61%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (dq, J = 2.9, 4.8 and 9.2 Hz, 1H), 7.71 (dd, J = 2.4 and 6.8 Hz, 1H), 7.64 (q, J = 8 and 14.8 Hz, 1H), 7.32 (t, J = 9.6 Hz, 1H), 7.04 (t, J = 8.8 Hz, 2H), 6.64 (s, 1H), 5.36 (s, 2H), 4.10 (s, 2H), 2.10 (s, 3H) ppm. ^{19} F NMR (400 MHz, CD_3OD) δ -111.54 (1F), -115.99 (1 F), -129.71 (1F) ppm. LC/MS, t_r = 5.04 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 498 (M+H).

Example 724



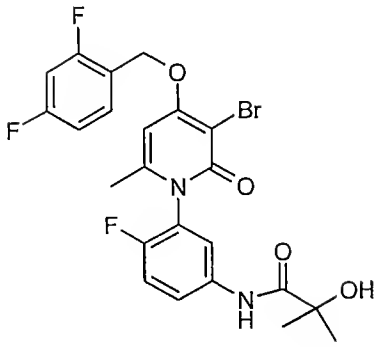
N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenyl}-2-hydroxy-2-methylpropanamide

Step 1 Preparation of 2-({3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenyl}amino)-1,1-dimethyl-2-oxoethyl acetate



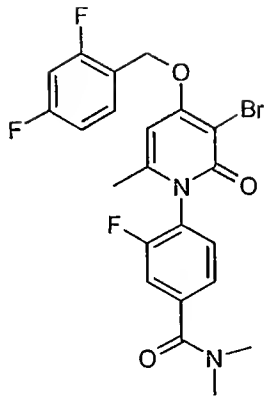
A solution of the compound of Example 722 (0.5 g, 1.05 mmol) in tetrahydrofuran (20 mL) was treated with triethyl amine (0.3 mL, 2.1 mmol) and 1-chlorocarbonyl-1-methylethyl acetate (0.16 mL, 1.15 mmol). After stirring at room temperature for 2h, the reaction was complete. The reaction mixture was poured into saturated aqueous ammonium chloride. The solids were filtered off and were washed with water and diethyl ether. The compound of Step 1 was isolated as a white solid (0.23 g, 39%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (m, 2H), 7.54 (dd, J = 2.8 and 6.8 Hz, 1H), 7.30 (t, J = 9.2 Hz, 1H), 7.04 (t, J = 9.2 Hz, 2H), 6.64 (s, 1H), 5.35 (s, 2H), 2.11 (s, 3H), 2.08 (s, 3H), 1.61 (s, 6H) ppm. ^{19} F NMR (400 MHz, CD_3OD) δ -111.57 (1F), -116.00 (1 F), -129.56 (1F) ppm. LC/MS, t_r = 5.65 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 568 (M+H).

Step 2 Preparation of N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenyl}-2-hydroxy-2-methylpropanamide



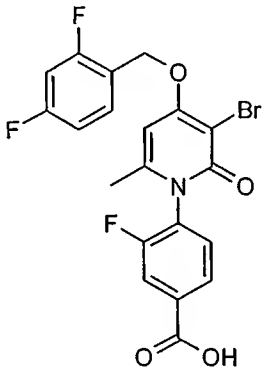
The product of Step 1 (0.1 g, 0.17mmol) was suspended in tetrahydrofuran (10 mL), methanol (2 mL), and 2.5 N NaOH (1 mL). After stirring at room temperature for 1 hour, the reaction was complete and the organics were removed *in vacuo*. The aqueous layer was acidified to pH 1 with 6N HCl, the solids were suspended in water, filtered, and washed with diethyl ether. The title compound was obtained as a white powder (56 mg, 61%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (dq, J = 2.8, 4.4 and 9.2 Hz, 1H), 7.69 (dd, J = 2.8 and 6.8 Hz, 1H), 7.64 (q, J = 8 and 14.8 Hz, 1H), 7.31 (t, J = 9.2 Hz, 1H), 7.04 (t, J = 8.4 Hz, 2H), 6.64 (s, 1H), 5.35 (s, 2H), 2.10 (s, 3H), 1.43 (s, 6H) ppm. ^{19} F NMR (400 MHz, CD_3OD) δ -111.55 (1F), -115.95 (1 F), -129.80 (1F) ppm. LC/MS, t_r = 5.34 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 526 (M+H).

Example 725



4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-fluoro-N,N-dimethylbenzamide

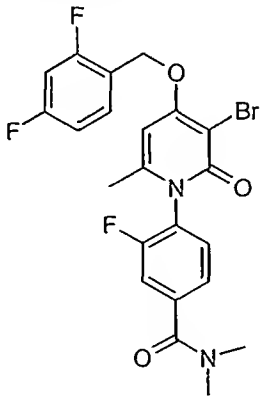
Step 1 Preparation of 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-fluorobenzoic acid



Compound of Example 604 (4.1 g, 8.5mmol) was suspended in tetrahydrofuran (30 mL), methanol (15 mL), water (15 mL) and 2.5 N NaOH (6.8 mL, 17 mmol)). After stirring at room temperature for 2 hour, the reaction was complete and the organics were removed. The aqueous layer was acidified to pH 1 with 3N HCl, the solids were suspended in water, filtered, and washed with diethyl ether. The title compound was obtained as a white powder and used without further purification (4.4 g). ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (dd, J = 1.8 and 8.8 Hz, 1H), 7.93 (dd, J = 1.48 and 10 Hz, 1H), 7.64 (q, J = 8 and 14.8 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.05 (t, J = 10 Hz, 2H), 6.66 (s, 1H), 5.36 (s, 2H), 2.08 (s, 3H) ppm. ^{19} F NMR (400 MHz, CD_3OD) δ -111.48 (1F), -115.96 (1 F), -

123.35 (1F) ppm. ES-HRMS *m/z* 468.9987 (M+H calcd for $C_{20}H_{14}BrF_3NO_4$ requires 469.0086).

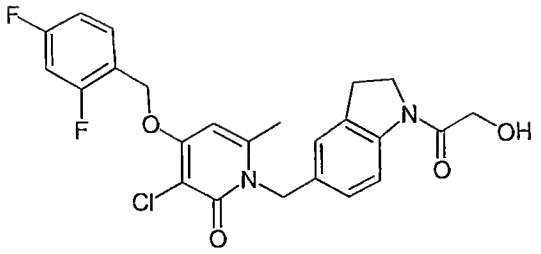
Step 2 Preparation of 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-fluoro-



N,N-dimethylbenzamide

A solution of the product of Step 1 (0.5 g, 1.07 mmol) in *N,N*-dimethyl formamide was cooled to 0 C. *Iso*-butyl chloroformate (0.14 mL, 1.07 mmol) and *N*-methyl morpholine (0.12 mL, 1.07 mmol) were added. After 20 minutes, *N,N*-dimethylamine (2.0 M, 1.1 mL, 2.14 mmol) was added and the reaction mixture was warmed to room temperature over 18 h. The reaction mixture was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organics were washed with brine and concentrated *in vacuo*. The resulting semi-solid was treated with ethyl acetate and acetone to precipitate the title compound (90 mg, 17%). ^{1}H NMR (400 MHz, dmso-d_6) δ 7.67 (q, J = 8 and 14.8 Hz, 1H), 7.52 (m, 2H), 7.35 (m, 2H), 7.18 (td, J = 2.8 and 8.8 Hz, 1H), 6.73 (s, 1H), 5.34 (s, 2H), 2.98 (s, 3H), 2.91 (s, 3H), 2.00 (s, 3H) ppm. ^{19} F NMR (400 MHz, dmso-d_6) δ -109.50 (1F), -113.63 (1 F), -122.09 (1F) ppm. ES-HRMS *m/z* 496.0570 (M+H calcd for $C_{22}H_{19}BrF_3N_2O_3$ requires 496.0558).

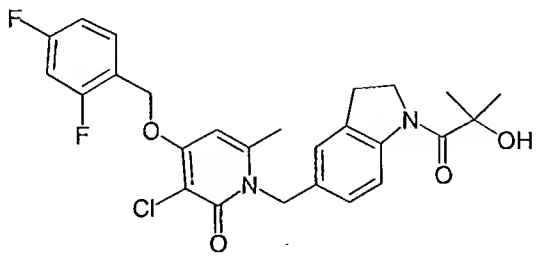
Example 726



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1-glycoloyl-2,3-dihydro-1H-indol-5-yl)methyl]-6-methylpyridin-2(1H)-one

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with compound of Example 633 (180 mg, 0.43 mmol), acetoxyacetyl chloride (51 μL, 0.47 mmol), triethylamine (119 μL, 0.86 mmol) and tetrahydrofuran (3.0 mL). After stirring at 25° C for 20 min the reaction was completed by LC-MS. NaOH (2.5M, 2.24 mmol, 1.0 mL) and MeOH (2.0mL) was added and stirred for 20 min to give the title compound.The compound precipitated out of solution. The precipitated was filtered and washed with water and diethyl ether to obtain the title compound (130 mg, 64%) as a white solid. ^{1}H NMR (400 MHz, (DMSO) δ 7.9 (d, *J* = 8.2, 1H), 7.6 (q, *J* = 8.5 and 6.9 Hz, 1H), 7.3 (t, *J* = 8.7 Hz, 1H), 7.1 (t, *J* = 7.9 Hz, 1H), 6.9 (s, 2H), 6.5 (s, 1H), 5.25 (s, 2H), 4.1 (d, *J* = 5.5 Hz, 2H), 3.9 (t, *J* = 8.6 Hz, 2H), 3.42 (t, *J* = 5.4 Hz, 1H), 3.35 (t, *J* = 4.8 Hz, 1H), 3.2 (t, *J* = 8.5 Hz, 2H), 2.3 (s, 3H) ppm. ES-HRMS *m/z* 475.1220 (M+H calcd for $C_{24}H_{22}ClF_2N_2O_4$ requires 475.1231).

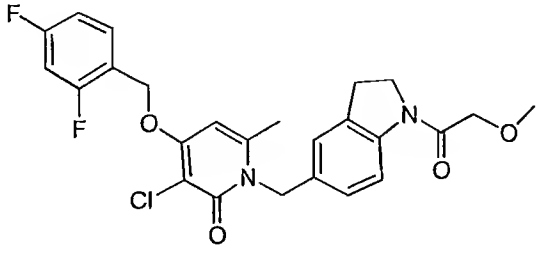
Example 727



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-indol-5-yl]methyl}-6-methylpyridin-2(1H)-one

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with compound of Example 633 (200 mg, 0.48 mmol), 1-chlorocarbonyl-1-methylethyl acetate (104.3 μL, 0.72 mmol), triethylamine (133 μL, 0.96 mmol) and tetrahydrofuran (4.0 mL). After stirring at 25° C for 20 min the reaction was completed by LC-MS. NaOH (2.5M, 2.24 mmol, 1.5 mL) and MeOH (2.0mL) was added and stirred for 20 min to give the title compound. The compound precipitated out of solution. The precipitate was filtered and washed with water and diethyl ether to obtain a white solid (240 mg, 99%). ^{1}H NMR (400 MHz, (DMSO) δ 8.0 (d, *J* = 8.3, 1H), 7.6 (q, *J* = 8.6 and 6.9 Hz, 1H), 7.3 (td, *J* = 2.5 and 7.8 Hz, 1H), 7.1 (td, *J* = 1.75 and 6.7 Hz, 1H), 6.95 (s, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.58 (s, 1H), 5.25 (s, 2H), 4.3 (t, *J* = 8.3 Hz, 2H), 3.42 (t, *J* = 5.4 Hz, 1H), 3.35 (t, *J* = 5.2 Hz, 1H), 3.0 (t, *J* = 8.2 Hz, 2H), 2.3 (s, 3H), 1.3 (s, 6H) ppm. ES-HRMS *m/z* 503.1561 (M+H calcd for $C_{26}H_{26}ClF_2N_2O_4$ requires 503.1544).

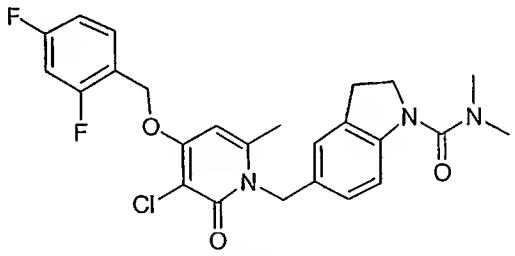
Example 728



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(methoxyacetyl)-2,3-dihydro-1H-indol-5-yl]methyl}-6-methylpyridin-2(1H)-one

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with compound of Example 633 (200 mg, 0.48 mmol), methoxyacetyl chloride (66 µL, 0.72 mmol), triethylamine (134 µL, 0.96 mmol) and tetrahydrofuran (4.0 mL). After stirring at 25° C for 20 min the reaction was completed by LC-MS. The compound precipitated out of solution. The precipitate was filtered and washed with water and diethyl ether to obtain a white solid (195 mg, 83%). ^{1}H NMR (400 MHz, (DMSO) δ 8.0 (d, *J* = 8.0, 1H), 7.6 (q, *J* = 8.6 and 6.7 Hz, 1H), 7.3 (td, *J* = 2.4 and 6.7 Hz, 1H), 7.1 (td, *J* = 1.88 and 6.6 Hz, 1H), 6.9 (s, 2H), 6.58 (s, 1H), 5.25 (s, 2H), 4.15 (s, 2H), 3.9 (t, *J* = 8.3 Hz, 2H), 3.45 (m, 1H), 3.4 (m, 1H), 3.32 (s, 3H), 3.0 (t, *J* = 8.5 Hz, 2H), 2.3 (s, 3H) ppm. ES-HRMS *m/z* 489.1387 (M+H calcd for $C_{25}H_{24}ClF_2N_2O_4$ requires 489.1387).

Example 729

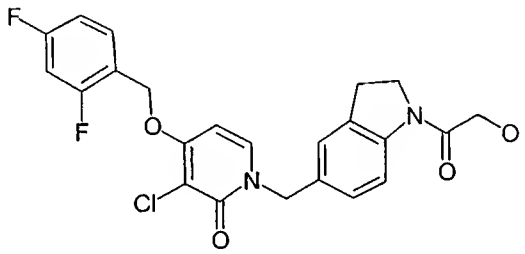


5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylindoline-1-carboxamide

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with compound of Example 633 (200 mg, 0.48 mmol), dimethylcarbamyl chloride (66 µL, 0.72 mmol), triethylamine (133 µL, 0.96 mmol) and tetrahydrofuran (4.0 mL). After stirring at 25° C for 5 min the reaction was completed by LC-MS. The compound precipitated out of solution. The

precipitate was filtered and washed with water and diethyl ether to obtain a white solid (198 mg, 85%). ^{1}H NMR (400 MHz, (DMSO) δ 7.6 (q, *J* = 7.4 Hz, 1H), 7.3 (t, *J* = 8.9 Hz, 1H), 7.1 (t, *J* = 8.5 Hz, 2H), 6.93 (s, 1H), 6.86 (s, 1H), 6.58 (s, 1H), 5.25 (s, 2H), 3.9 (t, *J* = 8.2 Hz, 2H), 3.45 (m, 1H), 3.4 (m, 1H), 2.9 (t, *J* = 8.3 Hz, 2H), 2.8 (s, 6H), 2.3 (s, 3H) ppm. ES-HRMS *m/z* 488.1548 (M+H calcd for $C_{25}H_{24}ClF_2N_2O_4$ requires 488.1547).

Example 730

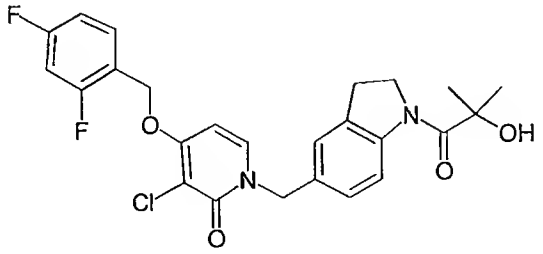


3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1-glycoloyl-2,3-dihydro-1H-indol-5-yl)methyl]pyridin-2(1H)-one

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with compound of Example 88 (200 mg, 0.5 mmol), acetoxyacetyl chloride (59 μL, 0.55 mmol), triethylamine (140 μL, 1.0 mmol) and tetrahydrofuran (3.0 mL). After stirring at 25° C for 20 min the reaction was completed by LC-MS. NaOH (2.5M, 2.24 mmol, 1.0 mL) and MeOH (2.0mL) was added and stirred for 20 min to give the title compound. The compound precipitated out of solution. The precipitated was filtered and washed with water and diethyl ether to obtain the title compound (200 mg, 83%) as a white solid. ^{1}H NMR (400 MHz, (DMSO) δ 7.98 (d, *J* = 8.1, 1H), 7.9 (d, *J* = 7.8 Hz, 1H), 7.6 (q, *J* = 8.6 and 6.6 Hz, 1H), 7.3 (dt, *J* = 2.4 and 7.2 Hz, 1H), 7.1 (m, 2H), 6.56 (d, *J* =7.8 Hz, 1H), 5.25 (s, 2H),5.1 (s, 2H), 4.8 (t, *J* = 5.8 Hz, 1H), 4.1 (d, *J* = 5.6 Hz, 2H), 3.9 (t,

J = 7.9 Hz, 2H), 3.1 (t, J = 7.9 Hz, 2H) ppm. ES-HRMS m/z 461.1088 (M+H calcd for $C_{23}H_{20}ClF_2N_2O_4$ requires 461.1074).

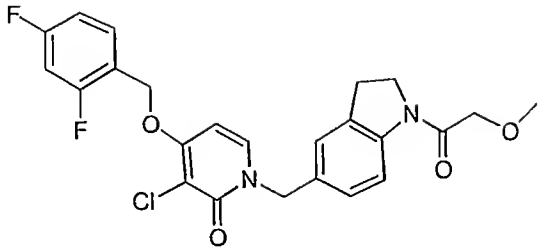
Example 731



Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1-glycoloyl-2,3-dihydro-1H-indol-5-yl)methyl]pyridin-2(1H)-one

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with compound of Example 88 (200 mg, 0.50 mmol), 1-chlorocarbonyl-1-methylethyl acetate (80 µL, 0.55 mmol), triethylamine (140 µL, 1.0 mmol) and tetrahydrofuran (4.0 mL). After stirring at 25° C for 20 min the reaction was completed by LC-MS. NaOH (2.5M, 2.24 mmol, 1.5 mL) and MeOH (2.0mL) was added and stirred for 20 min to give the title compound. The compound precipitated out of solution. The precipitated was filtered and washed with water and diethyl ether to obtain the title compound (136 mg, 55%) a white solid. ^{1}H NMR (400 MHz, (DMSO) δ 7.98 (d, J = 8.1, 1H), 7.9 (d, J = 7.8 Hz, 1H), 7.6 (q, J = 8.6 and 6.6 Hz, 1H), 7.3 (m, 1H), 7.1 (m, 2H), 6.56 (d, J =7.8 Hz, 1H), 5.25 (s, 2H),5.0 (s, 2H), 4.3 (t, J = 7.8 Hz, 2H), 3.0 (t, J = 7.9 Hz, 2H), 1.3 (s, 6H) ppm. ES-HRMS m/z 489.1376 (M+H calcd for $C_{25}H_{24}ClF_2N_2O_4$ requires 489.1387).

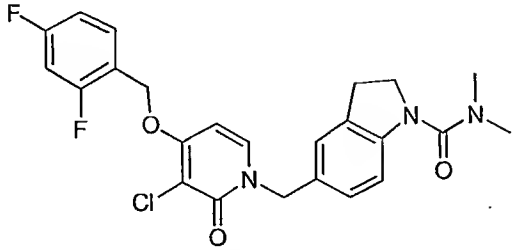
Example 732



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(methoxyacetyl)-2,3-dihydro-1H-indol-5-yl]methyl}pyridin-2(1H)-one

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the compound of Example 88 (200 mg, 0.5 mmol), methoxyacetyl chloride (69 μL, 0.75 mmol), triethylamine (139 μL, 1.0 mmol) and tetrahydrofuran (4.0 mL). After stirring at 25° C for 20 min the reaction was completed by LC-MS. The compound precipitated out of solution. The precipitate was filtered and washed with water and diethyl ether to obtain a white solid (195 mg, 83%). ^{1}H NMR (400 MHz, (DMSO) δ 7.98 (d, *J* = 8.2, 1H), 7.9 (d, *J* = 7.7 Hz, 1H), 7.6 (d, *J* = 8.5 Hz, 1H), 7.3 (t, *J* = 9.6 Hz, 1H), 7.1 (m, 3H), 6.56 (d, *J* =7.8 Hz, 1H), 5.25 (s, 2H),5.1 (s, 2H), 4.1 (s, 2H), 3.98 (t, *J* = 7.9 Hz, 2H), 3.33 (s, 3H), 3.0 (t, *J* = 7.9 Hz, 2H) ppm. ES-HRMS *m/z* 461.1088 (M+H calcd for $C_{23}H_{20}ClF_2N_2O_4$ requires 461.1074).

Example 733



5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]2-oxopyridin-1(2H)-yl]methyl}-N,
N-dimethylindoline-1-carboxamide

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the compound of Example 88 (200 mg, 0.5 mmol), dimethylcarbamyl chloride (69 µL, 0.75 mmol), triethylamine (139 µL, 1.0 mmol) and tetrahydrofuran (4.0 mL). After stirring at 25° C for 5 min the reaction was completed by LC-MS. The compound precipitated out of solution. The precipitate was filtered and washed with water and diethyl ether to obtain a white solid (188 mg, 58%). ^{1}H NMR (400 MHz, (DMSO) δ 7.9 (d, *J* = 8.1, 1H), 7.6 (q, *J* = 8.6 and 6.6 Hz, 1H), 7.3 (t, *J* = 9.3 Hz, 1H), 7.1 (m, 3H), 6.8 (d, *J* =8.0 Hz, 1H), 6.5 (d, *J* = 7.8 Hz, H), 5.25 (s, 2H),5.0 (s, 2H), 3.7 (t, *J* = 8.6 Hz, 2H), 2.9(t, *J* = 7.9 Hz, 2H), 2.8 (s, 6H) ppm. ES-HRMS *m/z* 474.1387 (M+H calcd for $C_{24}H_{23}ClF_2N_3O_3$ requires 474.1391).

BIOLOGICAL EVALUATION

p38 Kinase Assay

Cloning of human p38a:

The coding region of the human p38a cDNA was obtained by PCR-amplification from RNA isolated from the human monocyte cell line THP.1. First strand CDNA was synthesized from total RNA as follows: 2 µg of RNA was annealed to 100 ng of random hexamer primers in a 10 µl reaction by heating to 70° C. for 10 minutes followed by 2 minutes on ice. cDNA was then synthesized by adding 1 µl of RNAsin (Promega, Madison Wis.), 2 µl of 50 mM dNTP's, 4 µl of 5X buffer, 2 µl of 100 mM DTT and 1 µl (200 U) of Superscript II™ AMV reverse transcriptase. Random primer, dNTP's and Superscript II™ reagents were all purchased from Life-Technologies, Gaithersburg, Mass. The reaction was incubated at 42° C. for 1 hour. Amplification of p38 cDNA was performed by aliquoting 5 µl of the reverse

transcriptase reaction into a 100 μl PCR reaction containing the following: 80 μl dH.sub.2 O, 2 . μl 50 mM dNTP's, 1 μl each of forward and reverse primers (50 pmol/μl), 10 μl of 10X buffer and 1 μl Expand™ polymerase (Boehringer Mannheim). The PCR primers incorporated Bam HI sites onto the 5' and 3' end of the amplified fragment, and were purchased from Genosys. The sequences of the forward and reverse primers were 5'-GATCGAGGATTCATGTCTCAGGAGAGGCCCA-3' and 5'GATCGAGGATTCTCAGGACTCCATCTCTTC-3' respectively. The PCR amplification was carried out in a DNA Thermal Cycler (Perkin Elmer) by repeating 30 cycles of 94° C. for 1 minute, 60° C. for 1 minute and 68° C. for 2 minutes. After amplification, excess primers and unincorporated dNTP's were removed from the amplified fragment with a Wizard™ PCR prep (Promega) and digested with Bam HI (New England Biolabs). The Bam HI digested fragment was ligated into BamHI digested pGEX 2T plasmid DNA (PharmaciaBiotech) using T-4 DNA ligase (New England Biolabs) as described by T. Maniatis, Molecular Cloning: A Laboratory Manual, 2nd ed. (1989). The ligation reaction was transformed into chemically competent E. coli DH10B cells purchased from Life-Technologies following the manufacturer's instructions. Plasmid DNA was isolated from the resulting bacterial colonies using a Promega Wizard™ miniprep kit. Plasmids containing the appropriate Bam HI fragment were sequenced in a DNA Thermal Cycler (Perkin Elmer) with Prism™ (Applied Biosystems Inc.). cDNA clones were identified that coded for both human p38a isoforms (Lee et al. Nature 372, 739). One of the clones that contained the cDNA for p38a-2 (CSB-2) inserted in the cloning site of PGEX 2T, 3' of the GST coding region was designated pMON 35802. The sequence obtained for this clone is an exact match of the cDNA clone reported by

Lee et al. This expression plasmid allows for the production of a GST-p38a fusion protein.

Expression of human p38a

GST/p38a fusion protein w as expressed from the plasmid pMON 35802 in E. coli, stain DH10B (Life Technologies, Gibco-BRL). Overnight cultures were grown in Luria Broth (LB) containing 100 mg/ml ampicillin. The next day, 500 ml of fresh LB was inoculated with 10 ml of overnight culture, and grown in a 2 liter flask at 37° C. with constant shaking until the culture reached an absorbance of 0.8 at 600 nm. Expression of the fusion protein was induced by addition of isopropyl b-D-thiogalactosidase (IPTG) to a final concentration of 0.05 mM. The cultures were shaken for three hours at room temperature, and the cells were harvested by centrifugation. The cell pellets were stored frozen until protein purification.

Purification of P38 Kinase-alpha

All chemicals were from Sigma Chemical Co. unless noted. Twenty grams of E. coli cell pellet collected from five 1 L shake flask fermentations was resuspended in a volume of PBS (140 mM NaCl, 2.7 mM KCl, 10 mM Na.sub.2 HPO.sub.4, 1.8 mM KH.sub.2 PO.sub.4, pH 7.3) up to 200 ml. The cell suspension was adjusted to 5 mM DTT with 2 M DTT and then split equally into five 50 ml Falcon conical tubes. The cells were sonnicated (Ultrasonics model W375) with a 1 cm probe for 3.times.1 minutes (pulsed) on ice. Lysed cell material was removed by centrifugation (12,000 x g, 15 minutes) and the clarified supernatant applied to glutathione-sepharose resin (Pharmacia).

Glutathione-Sepharose Affinity Chromatography

Twelve ml of a 50% glutathione sepharose-PBS suspension was added to 200 ml clarified supernatant and incubated batchwise for 30 minutes at room temperature. The resin was collected by centrifugation (600.times.g, 5 min) and washed with 2.times.150 ml PBS/1% Triton X-100, followed by 4.times.40 ml PBS. To cleave the p38 kinase from the GST-p38 fusion protein, the glutathione-sepharose resin was resuspended in 6 ml PBS containing 250 units thrombin protease (Pharmacia, specific activity >7500 units/mg) and mixed gently for 4 hours at room temperature. The glutathione-sepharose resin was removed by centrifugation (600.times.g, 5 min) and washed 2.times.6 ml with PBS. The PBS wash fractions and digest supernatant containing p38 kinase protein were pooled and adjusted to 0.3 mM PMSF.

Mono Q Anion Exchange Chromatography

The thrombin-cleaved p38 kinase was further purified by FPLC-anion exchange chromatography. Thrombin-cleaved sample was diluted 2-fold with Buffer A (25 mM HEPES, pH 7.5, 25 mM beta-glycerophosphate, 2 mM DTT, 5% glycerol) and injected onto a Mono Q HR 10/10 (Pharmacia) anion exchange column equilibrated with Buffer A. The column was eluted with a 160 ml 0.1 M-0.6 M NaCl/Buffer A gradient (2 ml/minute flowrate). The p38 kinase peak eluting at 200 mM NaCl was collected and concentrated to 3-4 ml with a Filtron 10 concentrator (Filtron Corp.).

Sephacryl S100 Gel Filtration Chromatography

The concentrated Mono Q- p38 kinase purified sample was purified by gel filtration chromatography (Pharmacia HiPrep 26/60 Sephacryl S100 column equilibrated with Buffer B (50 mM HEPES, pH 7.5, 50 mM NaCl, 2 mM DTT, 5% glycerol)). Protein was eluted from the column with Buffer B at a 0.5 ml/minute flowrate and protein was detected by absorbance at 280 nm.

Fractions containing p38 kinase (detected by SDS-polyacrylamide gel electrophoresis) were pooled and frozen at -80° C. Typical purified protein yields from 5 L E. coli shake flasks fermentations were 35 mg p38 kinase.

In Vitro Assay

The ability of compounds to inhibit human p38 kinase alpha was evaluated using two in vitro assay methods. In the first method, activated human p38 kinase alpha phosphorylates a biotinylated substrate, PHAS-I (phosphorylated heat and acid stable protein-insulin inducible), in the presence of gamma ^{32}P-ATP (^{32}P-ATP). PHAS-I was biotinylated prior to the assay and provides a means of capturing the substrate, which is phosphorylated during the assay. p38 Kinase was activated by MKK6. Compounds were tested in 10 fold serial dilutions over the range of 100 μM to 0.001 μM using 1% DMSO. Each concentration of inhibitor was tested in triplicate.

All reactions were carried out in 96 well polypropylene plates. Each reaction well contained 25 mM HEPES pH 7.5, 10 mM magnesium acetate and 50 μM unlabeled ATP. Activation of p38 was required to achieve sufficient signal in the assay. Biotinylated PHAS-I was used at 1-2 μg per 50 μl reaction volume, with a final concentration of 1.5 μM. Activated human p38 kinase alpha was used at 1 μg per 50 μl reaction volume representing a final concentration of 0.3 μM. Gamma ^{32}P-ATP was used to follow the phosphorylation of PHAS-I. ^{32}P-ATP has a specific activity of 3000 Ci/mmol and was used at 1.2 μCi per 50 μl reaction volume. The reaction proceeded either for one hour or overnight at 30° C.

Following incubation, 20 μl of reaction mixture was transferred to a high capacity streptavidin coated filter plate (SAM-streptavidin-matrix, Promega) prewetted with

phosphate buffered saline. The transferred reaction mix was allowed to contact the streptavidin membrane of the Promega plate for 1-2 minutes. Following capture of biotinylated PHAS-I with ^{32}P incorporated, each well was washed to remove unincorporated ^{32}P-ATP three times with 2M NaCl, three washes of 2M NaCl with 1% phosphoric, three washes of distilled water and finally a single wash of 95% ethanol. Filter plates were air-dried and 20 μl of scintillant was added. The plates were sealed and counted.

A second assay format was also employed that is based on p38 kinase alpha induced phosphorylation of EGFRP (epidermal growth factor receptor peptide, a 21 mer) in the presence ^{33}P-ATP. Compounds were tested in 10 fold serial dilutions over the range of 100 μM to 0.001 μM in 1% DMSO. Each concentration of inhibitor was tested in triplicate. Compounds were evaluated in 50 μl reaction volumes in the presence of 25 mM Hepes pH 7.5, 10 mM magnesium acetate, 4% glycerol, 0.4% bovine serum albumin, 0.4mM DTT, 50 μM unlabeled ATP, 25 μg EGFRP (200 μM), and 0.05 μCi ^{33}P-ATP. Reactions were initiated by addition of 0.09 μg of activated, purified human GST-p38 kinase alpha. Activation was carried out using GST-MKK6 (5:1,p38:MKK6) for one hour at 30° C. in the presence of 50 μM ATP. Following incubation for 60 minutes at room temperature, the reaction was stopped by addition of 150 μl of AG 1.times.8 resin in 900 mM sodium formate buffer, pH 3.0 (1 volume resin to 2 volumes buffer). The mixture was mixed three times with pipetting and the resin was allowed to settle. A total of 50 μl of clarified solution head volume was transferred from the reaction wells to Microlite-2 plates. 150 μl of Microscint 40 was then added to each well of the Microlite plate, and the plate was sealed, mixed, and counted.

Representative compounds that exibit IC_{50} values between 1 and 25 μM (p38 alpha kinase assay) are: Example Nos. 20, 22, 23, 39, 43, 44, 48, 50, 52, 53, 55, 57, 58, 62, 92, 115, 118, 136, 139, 141, 142, 149, 156, 157, 169, 174, 219, 220, 244, 245, 387, 288, 289, 291, 292, 293, 294, 295, 296, 298, 297, 300, 301, 302 304, 305, 309, 310, 311, 323, 360, 394, 403, 414, 415, 416, 418, 420, 444, 447, 449, 451, 452, 471, 485, 486, 496, 498, 499, 503, 506, 561, 569, 574, 575 and 576.

Representatve compounds that exibit IC_{50} values between 25 and 100 μM (p38 alpha kinase assay) are: Example Nos. 1, 25, 33, 35, 37, 42, 45, 47, 49, 119, 204, 308, 558, 560, 564, 565, 566, 568 and 577.

Representatve compounds that exibit IC_{50} values less than 1 μM (p38 alpha kinase assay) are: Example Nos. 6, 14, 8, 17, 10, 15, 4, 117, 161, 162, 165, 170, 171, 172, 173 176, 179, 217, 218, 219, 220, 221, 223, 225, 230, 231, 234, 235, 272, 273, 275, 276, 278, 280, 282, 286, 285, 290, 312, 313, 314, 315, 316, 317, 318, 320, 321, 322, 364, 366, 400, 402, 405, 421, 422, 423, 446, 448, 450, 458, 466, 467, 468, 469, 470, 481, 482, 483, 484, 487, 489, 492, 493, 494, 495, 504, 521, 522, 523 557, 587, 589, 590, 591, 597, 609, 610, 613, 629, 642, and 643.

Representatve compounds that exibit IC_{50} values greater than 100 μM (p38 alpha kinase assay) are: Example Nos. 3, 11, 38, 56, 116, 121, 237, 236, 413, 497 and 578.

TNF Cell Assays

Method of Isolation of Human Peripheral Blood Mononuclear Cells:

Human whole blood was collected in Vacutainer tubes containing EDTA as an anticoagulant. A blood sample (7 ml) was carefully layered over 5 ml PMN Cell Isolation Medium (Robbins

Scientific) in a 15 ml round bottom centrifuge tube. The sample was centrifuged at 450-500.times.g for 30-35 minutes in a swing out rotor at room temperature. After centrifugation, the top band of cells were removed and washed 3 times with PBS w/o calcium or magnesium. The cells were centrifuged at 400 .times.g for 10 minutes at room temperature. The cells were resuspended in Macrophage Serum Free Medium (Gibco BRL) at a concentration of 2 million cells/mi.

LPS Stimulation of Human PBMs

PBM cells (0.1 ml, 2 million/ ml) were co-incubated with 0.1 ml compound (10-0.41 μM, final concentration) for 1 hour in flat bottom 96 well microtiter plates. Compounds were dissolved in DMSO initially and diluted in TCM for a final concentration of 0.1% DMSO. LPS (Calbiochem, 20 ng/ml, final concentration) was then added at a volume of 0.010 ml. Cultures were incubated overnight at 37° C. Supernatants were then removed and tested by ELISA for TNF-a and IL1-b. Viability was analyzed using MTS. After 0.1 ml supernatant was collected, 0.020 ml MTS was added to remaining 0.1 ml cells. The cells were incubated at 37° C. for 2-4 hours, then the O.D. was measured at 490-650 nM.

Maintenance and Differentiation of the U937 Human Histiocytic Lymphoma Cell Line

U937 cells (ATCC) were propagated in RPMI 1640 containing 10% fetal bovine serum, 100 IU/ml penicillin, 100 μg/ml streptomycin, and 2 mM glutamine (Gibco). Fifty million cells in 100 ml media were induced to terminal monocytic differentiation by 24 hour incubation with 20 ng/ml phorbol 12-myristate 13-acetate (Sigma). The cells were washed by centrifugation (200.times.g for 5 min) and resuspended in 100 ml fresh medium. After 24-48 hours, the cells were harvested,

centrifuged, and resuspended in culture medium at 2 million cells/ml.

LPS Stimulation of TNF production by U937 Cells

U937 cells (0.1 ml, 2 million/ml) were incubated with 0.1 ml compound (0.004-50 μM, final concentration) for 1 hour in 96 well microtiter plates. Compounds were prepared as 10 mM stock solutions in DMSO and diluted in culture medium to yield a final DMSO concentration of 0.1% in the cell assay. LPS (E coli, 100 ng/ml final concentration) was then added at a volume of 0.02 ml. After 4 hour incubation at 37° C., the amount of TNF-.alpha. released in the culture medium was quantitated by ELISA. Inhibitory potency is expressed as IC50 (μM).

Rat Assay

The efficacy of the novel compounds in blocking the production of TNF also was evaluated using a model based on rats challenged with LPS. Male Harlen Lewis rats [Sprague Dawley Co.] were used in this model. Each rat weighed approximately 300 g and was fasted overnight prior to testing. Compound administration was typically by oral gavage (although intraperitoneal, subcutaneous and intravenous administration were also used in a few instances) 1 to 24 hours prior to the LPS challenge. Rats were administered 30 μg/kg LPS [salmonella typhosa, Sigma Co.] intravenously via the tail vein. Blood was collected via heart puncture 1 hour after the LPS challenge. Serum samples were stored at -20° C. until quantitative analysis of TNF-.alpha. by Enzyme Linked-Immuno-Sorbent Assay ("ELISA") [Biosource]. Additional details of the assay are set forth in Perretti, M., et al., Br. J. Pharmacol.

(1993), 110, 868-874, which is incorporated by reference in this application.

Mouse Assay

Mouse Model of LPS-Induced TNF Alpha Production

TNF alpha was induced in 10-12 week old BALB/c female mice by tail vein injection with 100 ng lipopolysaccharide (from S. Typhosa) in 0.2 ml saline. One hour later mice were bled from the retroorbital sinus and TNF concentrations in serum from clotted blood were quantified by ELISA. Typically, peak levels of serum TNF ranged from 2-6 ng/ml one hour after LPS injection.

The compounds tested were administered to fasted mice by oral gavage as a suspension in 0.2 ml of 0.5% methylcellulose and 0.025% Tween 20 in water at 1 hour or 6 hours prior to LPS injection. The 1 hour protocol allowed evaluation of compound potency at Cmax plasma levels whereas the 6 hour protocol allowed estimation of compound duration of action. Efficacy was determined at each time point as percent inhibition of serum TNF levels relative to LPS injected mice that received vehicle only.

Induction and Assessment of Collagen-Induced Arthritis in Mice

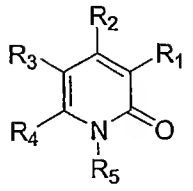
Arthritis was induced in mice according to the procedure set forth in J. M. Stuart, Collagen Autoimmune Arthritis, Annual Rev. Immunol. 2:199 (1984), which is incorporated herein by reference. Specifically, arthritis was induced in 8-12 week old DBA/1 male mice by injection of 50 μg of chick type II collagen (CII) (provided by Dr. Marie Griffiths, Univ. of Utah, Salt Lake City, Utah) in complete Freund's adjuvant (Sigma) on day 0 at the base of the tail. Injection volume was 100 μl. Animals were boosted on day 21 with 50 μg of CII in

incomplete Freund's adjuvant (100 μl volume). Animals were evaluated several times each week for signs of arthritis. Any animal with paw redness or swelling was counted as arthritic. Scoring of arthritic paws was conducted in accordance with the procedure set forth in Wooley et al., Genetic Control of Type II Collagen Induced Arthritis in Mice: Factors Influencing Disease Suspectibility and Evidence for Multiple MHC Associated Gene Control., Trans. Proc., 15:180 (1983). Scoring of severity was carried out using a score of 1-3 for each paw (maximal score of 12/mouse). Animals displaying any redness or swelling of digits or the paw were scored as 1. Gross swelling of the whole paw or deformity was scored as 2. Ankylosis of joints was scored as 3. Animals were evaluated for 8 weeks. 8-10 animals per group were used.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein

R_1 is H, halogen, NO_2, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, -CN, aryl, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN, haloalkyl, haloalkoxy or CO_2R;

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, or C_3-C_7 cycloalkyl;

R_2 is H, OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthio, arylthioalkoxy, arylalkynyl, alkoxy, aryloxy(C_1-C_6)alkyl, alkyl, alkynyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, alkoxyalkoxy, dialkylamino, alkyl, alkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylalkenyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxyalkoxy, NR_8R_9, dialkylamino, or CO_2R, wherein

n is 0, 1, 2, 3, 4, 5 or 6;

each of which groups is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently

halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, haloalkyl, heteroaryl, heteroarylalkyl, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, -(C_1-C_4)alkyl-C(O)NR_6R_7, -(C_1-C_4 alkyl)-NRC(O)$NR_{16}R_{17}$, haloalkoxy, alkyl, CN, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxycarbonyl, phenyl, -SO_2-phenyl wherein the phenyl and -SO_2-phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or NO_2, or -OC(O)NR_6R_7, wherein R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17} and the nitrogen to which they are attached form a morpholinyl ring;

R_6 and R_7 are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkanoyl, arylalkyl, arylalkoxy, alkoxycarbonyl, -SO_2-alkyl, OH, alkoxy, alkoxyalkyl, arylalkoxycarbonyl, -(C_1-C_4)alkyl-CO_2-alkyl, heteroarylalkyl, or arylalkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, heterocycloalkyl, heterocycloalkylalkyl, C_3-C_7 cycloalkyl, alkoxy, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-alkanoyl, alkyl, haloalkyl, carboxaldehyde, or haloalkoxy; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, pyrrolidinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, alkoxycarbonyl,

C_1-C_4 alkoxy, hydroxyl, hydroxyalkyl, dihydroxyalkyl, or halogen;

R at each occurrence is independently hydrogen or C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

R_{30} is C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

each R_8 is independently hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl;

each R_9 is hydrogen, alkyl, alkanoyl, arylalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, arylalkanoyl, -SO_2-phenyl, and aryl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl;

R_3 is H, halogen, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, -OC(O)NH$(CH_2)_n$aryl, arylalkoxy, -OC(O)N(alkyl)$(CH_2)_n$aryl, aryloxy, arylthio, thioalkoxy, arylthioalkoxy, alkenyl, -NR_6R_7, NR_6R_7-(C_1-C_6)alkyl, or alkyl, wherein

the aryl portion of arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, -OC(O)NH$(CH_2)_n$aryl, arylalkoxy, -OC(O)N(alkyl)$(CH_2)_n$aryl, and arylthioalkoxy, is unsubstituted or substituted with 1, 2, 3, 4, or 5

groups that are independently, halogen, alkoxy, alkyl, haloalkyl, or haloalkoxy,

wherein n is 0, 1, 2, 3, 4, 5, or 6; or

R_4 is hydrogen or R_4 is alkyl unsubstituted or substituted with one or two groups that are independently CO_2R, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, arylalkoxy, arylalkyl, heteroaryl, heteroarylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, $R_6R_7N-(C_1-C_6$ alkyl)-, $-NR_6R_7$, alkoxy, carboxaldehyde, $-C(O)NR_6R_7$, CO_2R, alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or aryl portions of is the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy; and

R_5 is H, aryl, arylalkyl, arylthioalkyl, alkyl optionally substituted with 1, 2, or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, C_3-C_7 cycloalkyl, or alkanoyl, alkoxy, alkoxyalkyl optionally substituted with one trimethylsilyl group, amino, alkoxycarbonyl, hydroxyalkyl, dihydroxyalkyl, alkynyl, $-SO_2$-alkyl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -alkyl-S-aryl, -alkyl-SO_2-aryl, heteroarylalkyl, heterocycloalkyl, heteroaryl, or alkenyl optionally substituted with alkoxycarbonyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, CO_2R, CN, OH, hydroxyalkyl, dihydroxyalkyl, amidinooxime, $-NR_6R_7$, $-NR_8R_9$, R_6R_7N-

(C_1-C_6 alkyl)-, carboxaldehyde, SO_2alkyl, -SO_2H, -$SO_2NR_6R_7$, alkanoyl wherein the alkyl portion is optionally substituted with OH, halogen or alkoxy, -$C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, amidino, haloalkyl, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$, -O-CH_2-O, -O-CH_2CH_2-O-, or haloalkoxy; wherein

R_{15} is H or C_1-C_6 alkyl; and

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

2. A compound according to claim 1, of the formula:

or a pharmaceutically acceptable salt thereof, wherein

R_1 is H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN, haloalkyl, haloalkoxy or CO_2R;

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups

that are independently halogen, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, or cyclopropyl;

R_2 is H, OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthioalkoxy, arylalkynyl, alkoxy, phenyloxy(C_1-C_6)alkyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, alkyl, alkynyl, alkoxyalkoxy, dialkylamino, heteroaryl, heterocycloalkyl, aryloxyalkyl, or CO_2R, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-NR_6R_7$, haloalkyl, haloalkoxy, alkyl, heteroaryl, heteroarylalkyl, $-(C_1-C_4)$alkyl-$C(O)NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)-$NRC(O)NR_{16}R_{17}$, CN, hydroxyalkyl, dihydroxyalkyl, $-OC(O)NR_6R_7$, or $-(C_1-C_6)$alkyl-$N(R)-CO_2R_{30}$, wherein

R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17} and the nitrogen to which they are attached form a morpholinyl ring;

R_6 and R_7 are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxyalkyl, alkanoyl, arylalkyl, arylalkoxy, arylalkoxycarbonyl, or arylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, OH, SH, carboxaldehyde, haloalkyl, or haloalkoxy; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, alkoxycarbonyl,

hydroxyl, hydroxyalkyl, dihydroxyalkyl, or halogen;

n is 0, 1, 2, 3, 4, 5 or 6;

R at each occurrence is independently H or C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

R_{30} is C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

R_4 is H, alkyl optionally substituted with one or two groups that are independently CO_2R, $-CO_2$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, arylalkoxy, heteroaryl, arylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, $-NR_6R_7$, $-C(O)NR_6R_7$, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or aryl portions of the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy; and

R_5 is H, arylalkyl, alkyl optionally substituted with 1, 2, or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, alkoxyalkyl optionally substituted with one trimethylsilyl group, alkoxycarbonyl, amino, hydroxyalkyl, dihydroxyalkyl, alkenyl optionally substituted with alkoxycarbonyl, alkynyl, $-SO_2$-alkyl, aryl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, heteroarylalkyl, heterocycloalkyl, or heteroaryl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, arylalkoxy, hydroxyalkyl, dihydroxyalkyl, thioalkoxy, $-SO_2$alkyl, alkoxycarbonyl, arylalkoxycarbonyl, CO_2R, CN, OH, amidinooxime, NR_8R_9, R_6R_7N-(C_1-C_6 alkyl)-, $-C(O)NR_6R_7$, amidino, hydroxyalkyl, dihydroxyalkyl, carboxaldehyde, $-NR_6R_7$, haloalkyl, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, -(C_1-C_4 alkyl)-CO_2R, -(C_1-C_4 alkyl)-C_1-C_6 alkoxycarbonyl, -(C_1-C_4 alkyl)-CN, -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$, $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, phenyl or haloalkoxy;

R_8 is hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl;

R_9 is alkyl, alkanoyl, arylalkyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, and arylalkanoyl.

3. A compound according to claim 2 wherein

R_1 is H, halogen, alkyl optionally substituted with C_1-C_4 alkoxycarbonyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, phenyl(C_1-C_6)alkoxy, phenyl(C_1-C_6)alkyl, CN, alkanoyl, alkoxy, C_2-C_4 alkynyl, C_2-C_6 alkenyl optionally substituted with C_1-C_4 alkoxycarbonyl, alkoxyalkyl, haloalkyl, or phenyl(C_1-C_6)alkanoyl,

wherein the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN, CF_3, OCF_3 or CO_2R;

wherein the alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy;

R_2 is OH, phenyl(C_1-C_6)alkoxy, phenyloxy, phenyloxy(C_1-C_6)alkyl, phenyl (C_1-C_4) thioalkoxy, C_1-C_8 alkoxy, alkoxyalkoxy, -O-SO_2phenyl, alkynyl, phenyl (C_2-C_4) alkynyl, alkyl, -OC(O)NH(CH_2)$_n$phenyl, -OC(O)N(alkyl)(CH_2)$_n$phenyl, dialkylamino, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrazolyl, pyrazinyl, benzimidazolyl, triazinyl, tetrahydrofuryl, piperidinyl, hexahydropyrimidinyl, thiazolyl, thienyl, or CO_2R, wherein n is 0, 1, 2, 3, 4, 5 or 6;

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, NR_6R_7, haloalkyl, haloalkoxy, hydroxyalkyl, dihydroxyalkyl, alkyl, phenyl, pyridyl, piperidinyl, piperazinyl, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, R_6R_7N-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, -(C_1-C_4)alkyl-C(O)NR_6R_7, -(C_1-C_4 alkyl)-NRC(O)$NR_{16}R_{17}$, or -OC(O)NR_6R_7, wherein

R_6 and R_7 are independently at each occurrence H, alkyl, (C_1-C_4) hydroxyalkyl, (C_1-C_4) dihydroxyalkyl, (C_1-C_4) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkanoyl, phenyl (C_1-C_4) alkyl, phenyl (C_1-C_4) alkoxy, phenyl (C_1-C_4) alkoxycarbonyl, or phenyl (C_1-C_4) alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) alkyl, CF_3, carboxaldehyde, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl (C_1-C_6)alkyl, OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2

groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxycarbonyl, or halogen; and

R_4 is H, alkyl optionally substituted with one or two groups that are independently CO_2R, $-CO_2$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, $-C(O)NR_6R_7$, phenyl(C_1-C_6)alkoxy, phenyl(C_1-C_6)alkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein

the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, CF_3, OCF_3;

R_5 is phenyl(C_1-C_6)alkyl, (C_1-C_6)alkyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently phenyl C_1-C_4 alkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, phenyl, alkoxy, C_2-C_6 alkynyl, C_2-C_6 alkenyl optionally substituted with alkoxycarbonyl, indolyl, quinolinyl, isoquinolinyl, isoindolyl, dihydroindolyl, pyrazolyl, imidazolyl, dihydroisoindolyl, indolon-2-yl, indazolyl, benzimidazolyl, pyridyl, imidazolidine dione, pyrazolyl$(C_1-C_6$ alkyl), imidazolyl$(C_1-C_6$ alkyl), piperidinyl(C_1-C_6)alkyl, pyrrolidinyl(C_1-C_6)alkyl, imidazolidinyl(C_1-C_6)alkyl, tetrahydroisoquinolinyl(C_1-C_6)alkyl, 1H-indazolyl(C_1-C_6)alkyl, dihydroindolon-2-yl$(C_1-C_6$ alkyl), indolinyl$(C_1-C_6$ alkyl), dihydrobenzimidazolyl$(C_1-C_6$ alkyl), or dihydrobenzoimidazolonyl$(C_1-C_6$ alkyl), pyridyl (C_1-C_6) alkyl, pyridazinyl (C_1-C_6) alkyl, pyrimidinyl (C_1-C_6) alkyl, pyrazinyl (C_1-C_6) alkyl, tetrahydrofuryl(C_1-C_6)alkyl, naphthyl(C_1-C_6)alkyl, morpholinyl (C_1-C_6) alkyl, tetrahydrofuryl (C_1-C_6) alkyl, thienyl (C_1-C_6) alkyl,

piperazinyl (C_1-C_6) alkyl, indolyl (C_1-C_6) alkyl, quinolinyl(C_1-C_6) alkyl, isoquinolinyl(C_1-C_6) alkyl, isoindolyl(C_1-C_6) alkyl, dihydroindolyl(C_1-C_6) alkyl, pyrazolyl(C_1-C_4) alkyl, imidazolyl(C_1-C_4) alkyl, dihydroisoindolyl(C_1-C_6) alkyl, indoon-2-yl(C_1-C_6) alkyl, indolon-2-yl(C_1-C_6) alkyl, or morpholinyl C_1-C_6 alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, phenyl C_1-C_6 alkoxy, C_1-C_6 thioalkoxy, C_1-C_6 alkoxycarbonyl, CO_2R, CN, $-SO_2(C_1$-$C_6)$alkyl, amidinooxime, NR_8R_9, $-NR_6R_7$, NR_6R_7 C_1-C_6 alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, amidino, C_1-C_4 haloalkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 dihydroxyalkyl, or C_1-C_4 haloalkoxy; wherein

R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl and phenyl C_1-C_6 alkanoyl; and

R_9 is aminoalkyl, mono C_1-C_6 alkylamino C_1-C_6 alkyl, di C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl, indazolyl, and phenyl C_1-C_6 alkanoyl.

4. A compound according to claim 3, wherein

R_1 is H, halogen, C_1-C_4 alkyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_4 alkenyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_4 alkynyl, or carboxaldehyde;

R_2 is benzyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, phenyl (C_1-C_4) thioalkoxy, or pyridyl; wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-(C_1$-$C_6)$alkyl-$N(R)$-CO_2R_{30}, NR_6R_7, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, (C_1-C_4) haloalkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)-$NRC(O)NR_{16}R_{17}$, (C_1-C_4) haloalkoxy,

hydroxyalkyl, C_1-C_6 dihydroxyalkyl, (C_1-C_6) alkyl, pyridyl, or R_6R_7N-(C_1-C_6 alkyl)-.

5. A compound according to claim 4, wherein

R_5 is indolyl, pyridyl, pyridazinyl, pyrimidinyl, indazolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, pyrazolyl, imidazolyl, furanyl, quinolinyl, isoquinolinyl, isoindolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, 4 or 5 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, $-CO_2CH_3$, C_1-C_4 hydroxyalkyl, dihydroxyalkyl, C_1-C_4 alkoxy, $-CO_2$(C_1-C_5 alkyl), benzyloxy, $-NR_6R_7$, -(C_1-C_4)alkyl-$C(O)NR_6R_7$, $-NR_8R_9$, NR_6R_7-(C_1-C_4 alkyl), $-C(O)NR_6R_7$, or amidinooxime; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl C_1-C_4 alkyl, phenyl C_1-C_4 alkoxy, or phenyl C_1-C_4 alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, aryl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

6. A compound according to claim 5, wherein

R_5 is indolyl, pyridyl, pyrimidinyl, pyrazolyl, furanyl, indazolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, or pyrazinyl, each of which is unsubstituted or

substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, $-CO_2CH_3$, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxy, $-CO_2(C_1$-C_5 alkyl), benzyloxy, $-C(O)NR_6R_7$, $-NR_8R_9$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $-NR_6R_7$, NR_6R_7-$(C_1$-C_4 alkyl)-, and amidinooxime.

7. A compound according to claim 6, wherein

R_5 is indolyl, pyridyl, pyrimidinyl, dihydroindolyl, dihydroisoindolyl, pyrazolyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, $-CO_2CH_3$, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxy, $-CO_2(C_1$-C_5 alkyl), benzyloxy, $-C(O)NR_6R_7$, NR_8R_9, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $-NR_6R_7$, NR_6R_7-$(C_1$-C_4 alkyl)-, or amidinooxime; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkanoyl, C_1-C_4 alkoxy C_1-C_4 alkyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

8. A compound according to claim 7, wherein

R_5 is indolyl, pyridyl, pyrimidinyl, dihydroindolyl, dihydroisoindolyl, pyrazolyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxy, $-C(O)NR_6R_7$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, NR_8R_9, $-NR_6R_7$, or NR_6R_7-$(C_1$-C_4 alkyl)-; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkanoyl, or C_1-C_4 alkoxy, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

9. A compound according to claim 4, wherein

R_5 is phenyl, phenyl(C_1-C_6)alkyl, or (C_1-C_6)alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, hydroxyalkyl, dihydroxyalkyl, thioalkoxy, -CO_2(C_1-C_5 alkyl), CO_2R, CN, amidinooxime, -NR_8R_9, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, -(C_1-C_4)alkyl-C(O)NR_6R_7, amidino, CF_3, or OCF_3;

R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl and phenyl C_1-C_6 alkanoyl; and

R_9 is aminoalkyl, mono C_1-C_6 alkylamino C_1-C_6 alkyl, di C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_4 alkyl, indazolyl, and phenyl C_1-C_4 alkanoyl.

10. A compound according to claim 4, wherein

R_5 is phenyl, phenyl(C_1-C_6)alkyl, which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, thioalkoxy, -CO_2(C_1-C_5 alkyl), CO_2R, CN, amidinooxime, -NR_8R_9, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, -(C_1-C_4)-C(O)NR_6R_7, amidino, CF_3, or OCF_3; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkanoyl,

phenyl C_1-C_4 alkyl, phenyl C_1-C_4 alkoxy, or phenyl C_1-C_4 alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl and phenyl C_1-C_6 alkanoyl; and

R_9 is aminoalkyl, mono C_1-C_6 alkylamino C_1-C_6 alkyl, di C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_4 alkyl, indazolyl, and phenyl C_1-C_4 alkanoyl.

11. A compound according to claim 10, wherein

R_5 is phenyl, benzyl or phenethyl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, $-NR_6R_7$, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, $-NR_8R_9$, halogen, C_1-C_6 alkoxy, CO_2R, $-(C_1$-C_4 alkyl$)-CO_2R$, C_1-C_6 thioalkoxy, amidinooxime, C_1-C_6 alkoxycarbonyl, $-(C_1$-C_4 alkyl$)-C_1$-C_6 alkoxycarbonyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, $-(C_1$-C_4 alkyl$)-CN$, CN, phenyl C_1-C_6 alkoxy, OH, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, $R_6R_7N-(C_1$-C_6 alkyl$)-$, $-(C_1$-C_4 alkyl$)-NR_{15}C(O)R_{18}$, amidinooxime, $-SO_2(C_1$-C_6 alkyl$)$, $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, phenyl C_1-C_4 alkoxy, or phenyl; wherein

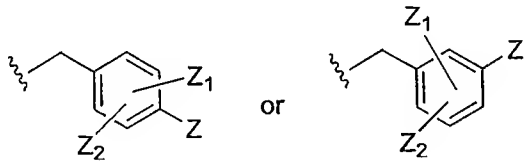
R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkanoyl, or C_1-C_4 alkoxy, each of which is optionally substituted with 1, 2, or 3 groups that

are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

12. A compound according to claim 11, wherein R_5 is phenyl, benzyl or phenethyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently CN, halogen, C_1-C_4 alkoxy, CF_3, OCF_3, C_1-C_4 alkyl, $-NR_8R_9$, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkanoyl, or C_1-C_4 alkoxy, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

13. A compound according to claim 4, wherein the R_5 group is of the formula:



wherein

Z_1 and Z_2 are independently H, halogen, C_1-C_4 alkyl, or CO_2R; and

Z is $-C(O)NR_6R_7$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)-$NR_{15}C(O)R_{18}$, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, $-NR_8R_9$, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkyl, CO_2R, or halogen; wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, or -

$SO_2(C_1\text{-}C_6$ alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3\text{-}C_6$ cycloalkyl, $C_1\text{-}C_4$ alkoxy, $C_1\text{-}C_4$ alkyl, OH, CF_3, or OCF_3;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl, thiomorpholinyl, ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ dihydroxyalkyl, or halogen; and

R_{18} is $C_1\text{-}C_6$ alkyl optionally substituted with $-O-(C_2\text{-}C_6$ alkanoyl, $C_1\text{-}C_6$ hydroxyalkyl, $C_1\text{-}C_4$ dihydroxyalkyl, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkoxy $C_1\text{-}C_6$ alkyl; amino $C_1\text{-}C_6$ alkyl, mono or dialkylamino $C_1\text{-}C_6$ alkyl.

14. A compound according to claim 4, wherein

R_5 is pyrazolyl($C_1\text{-}C_6$ alkyl), imidazolyl($C_1\text{-}C_6$ alkyl), thienyl($C_1\text{-}C_6$ alkyl), furanyl($C_1\text{-}C_6$ alkyl), piperidinyl($C_1\text{-}C_6$)alkyl, pyrrolidinyl($C_1\text{-}C_6$)alkyl, imidazolidinyl($C_1\text{-}C_6$)alkyl, piperazinyl($C_1\text{-}C_6$)alkyl, pyridyl($C_1\text{-}C_6$)alkyl, pyrimidyl($C_1\text{-}C_6$)alkyl, pyridazyl($C_1\text{-}C_6$)alkyl, pyrazinyl($C_1\text{-}C_6$)alkyl, isoquinolinyl($C_1\text{-}C_6$)alkyl, tetrahydroisoquinolinyl($C_1\text{-}C_6$)alkyl, indolyl($C_1\text{-}C_6$)alkyl, 1H-indazolyl($C_1\text{-}C_6$)alkyl, dihydroindolyl($C_1\text{-}C_6$ alkyl), dihydroindolon-2-yl($C_1\text{-}C_6$ alkyl), indolinyl($C_1\text{-}C_6$ alkyl), dihydroisoindolyl($C_1\text{-}C_6$ alkyl), dihydrobenzimdazolyl($C_1\text{-}C_6$ alkyl), or dihydrobenzoimidazolonyl($C_1\text{-}C_6$ alkyl), wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently ($C_1\text{-}C_6$)alkyl, halogen, ($C_1\text{-}C_6$)alkoxy, ($C_1\text{-}C_6$)hydroxyalkyl, $C_1\text{-}C_6$ dihydroxyalkyl, phenyl($C_1\text{-}C_6$)alkoxy, ($C_1\text{-}C_6$)thioalkoxy, ($C_1\text{-}C_6$)alkoxycarbonyl, phenyl($C_1\text{-}$

C_6)alkoxycarbonyl, OH, CO_2R, CN, amidinooxime, $-NR_8R_9$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, amidino, piperazinyl, morpholinyl, $-SO_2$ (C_1-C_6) alkyl, $-SO_2NH_2$, $-SO_2NH(C_1-C_6)$alkyl, $-SO_2N(C_1-C_6)$alkyl (C_1-C_6)alkyl, (C_1-C_4)haloalkyl, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)NR_{16}R_{17}$, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, or (C_1-C_4)haloalkoxy; wherein

R_6 and R_7 are independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)hydroxyalkyl, C_1-C_6 dihydroxyalkyl, $-(C_1-C_4)$alkyl$-CO_2-(C_1-C_6)$alkyl, (C_1-C_6)alkanoyl, phenyl(C_1-C_6)alkyl, phenyl(C_1-C_6)alkoxy, or phenyl(C_1-C_6)alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, (C_1-C_4)alkoxy, OH, SH, C_3-C_6 cycloalkyl, NH_2, $NH(C_1-C_6$ alkyl), $N(C_1-C_6$ alkyl$)(C_1-C_6$ alkyl), (C_1-C_4)alkyl, CF_3 or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen; and

R_{18} is C_1-C_6 alkyl optionally substituted with $-O-(C_2-C_6$ alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl,

15. A compound according to claim 14, wherein

R_5 is pyrazolyl(C_1-C_6 alkyl), imidazolyl(C_1-C_6 alkyl), benzimidazolyl(C_1-C_6 alkyl), thienyl(C_1-C_6 alkyl), pyrimidyl(C_1-C_6)alkyl, indolyl(C_1-C_6 alkyl), dihydroindolyl(C_1-C_6 alkyl), dihydroisoindolyl(C_1-C_6 alkyl), dihydroindolon-2-yl(C_1-C_6 alkyl), pyridinyl(C_1-C_6 alkyl), piperazinyl(C_1-C_6 alkyl), or pyrazinyl(C_1-C_6 alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, halogen, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, C_1-C_6 alkoxycarbonyl, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, haloalkyl, C_1-C_6 alkanoyl,

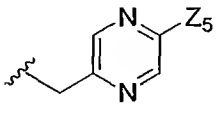
R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

16. A compound according to claim 15, wherein

R_5 is of the formula:



wherein

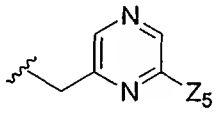
Z_5 is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, halogen, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, C_1-C_6 alkoxycarbonyl, R_6R_7N-(C_1-C_6 alkyl)-, -NR_6R_7, CF_3, or C_1-C_6 alkanoyl, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

17. A compound according to claim 15, wherein R_5 is of the formula:



wherein

Z_5 is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, halogen, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, C_1-C_6 alkoxycarbonyl, $R_6R_7N-(C_1$-C_6 alkyl$)-$, $-NR_6R_7$, CF_3, or C_1-C_6 alkanoyl, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

18. A compound according to either claim 16 or 17, wherein

Z_5 is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, halogen, C_1-C_6 alkoxycarbonyl, CF_3, or C_1-C_6 alkanoyl.

19. A compound according to either claim 16 or 17, wherein

Z_5 is C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, $R_6R_7N-(C_1$-C_6 alkyl$)-$, or $-NR_6R_7$, CF_3, or C_1-C_4 alkanoyl, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

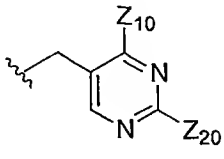
R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

20. A compound according to claim 19, wherein

Z_5 is $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, $R_6R_7N-(C_1$-C_6 alkyl$)-$, or $-NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, cyclopropyl, OH, SH, or C_1-C_4 alkoxy.

21. A compound according to claim 15, wherein

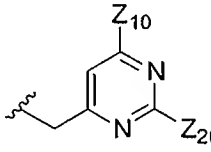
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, haloalkyl, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-C(O)NR_6R_7, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

22. A compound according to claim 15, wherein

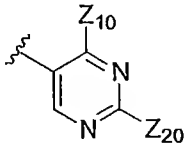
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-C(O)NR_6R_7, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

23. A compound according to claim 15, wherein

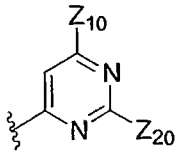
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, haloalkyl, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-C(O)NR_6R_7, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

24. A compound according to claim 15, wherein

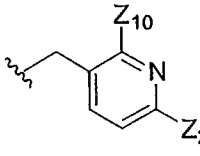
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-C(O)NR_6R_7, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

25. A compound according to claim 15, wherein

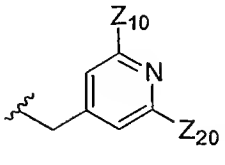
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, haloalkyl, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-C(O)NR_6R_7, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

26. A compound according to claim 15, wherein

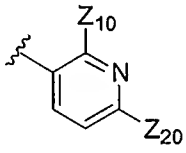
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

27. A compound according to claim 15, wherein

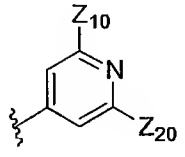
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, haloalkyl, (C_1-C_4)alkyl, OCF_3, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

28. A compound according to claim 15, wherein

R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, or -$C(O)NR_6R_7$, wherein R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

29. A compound according to claim 4, wherein R_5 is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, -$C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, -NR_6R_7, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, CF_3, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$; wherein

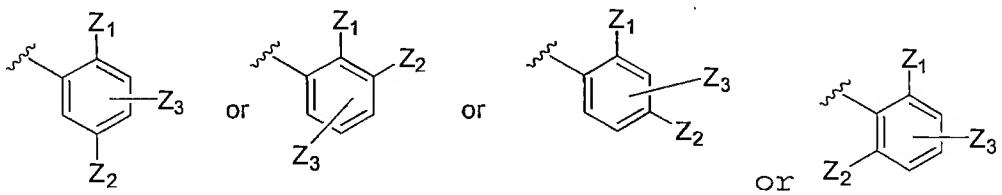
R_{15} is H or C_1-C_6 alkyl;

R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17}, and the nitrogen to which they are attached form a morpholinyl ring; and

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

30. A compound according to claim 29, wherein R_5 is of the formula:



Z_1 is H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, or C_1-C_4 alkoxy; and

Z_2 is C_1-C_4 alkyl, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, -NR_6R_7, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, or C_1-C_4 haloalkyl;

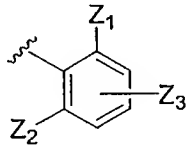
Z_3 is H, C_1-C_4 alkyl, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, -NR_6R_7, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, or C_1-C_4 haloalkyl;

wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, -SO_2(C_1-C_6 alkyl), -SO_2NH_2, -SO_2NH(C_1-C_6 alkyl), -SO_2N(C_1-C_6 alkyl)(C_1-C_6 alkyl), or C_1-C_6 alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

31. A compound according to claim 30, wherein

R_5 is of the formula:



wherein

Z_1 is H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl; C_1-C_4 dihydroxyalkyl, or C_1-C_4 alkoxy; and

Z_2 is C_1-C_4 alkyl, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, -NR_6R_7, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, or C_1-C_4 haloalkyl;

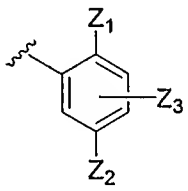
Z_3 is H, C_1-C_4 alkyl, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, -NR_6R_7, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6

dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, or C_1-C_4 haloalkyl, wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, -SO_2(C_1-C_6 alkyl), -SO_2NH_2, -SO_2NH(C_1-C_6 alkyl), -SO_2N(C_1-C_6 alkyl)(C_1-C_6 alkyl), or C_1-C_6 alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

32. A compound according to claim 30, wherein

R_5 is of the formula:



wherein

Z_1 is H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, or C_1-C_4 alkoxy; and

Z_2 is C_1-C_4 alkyl, -$C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, -NR_6R_7, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, or C_1-C_4 haloalkyl;

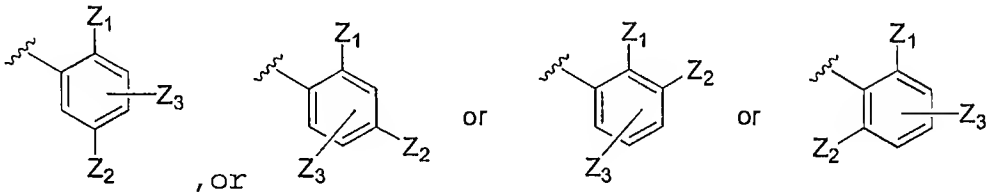
Z_3 is H, C_1-C_4 alkyl, -$C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, -NR_6R_7, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, or C_1-C_4 haloalkyl, wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl,

C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, -SO_2(C_1-C_6 alkyl), -SO_2NH_2, -SO_2NH(C_1-C_6 alkyl), -SO_2N(C_1-C_6 alkyl)(C_1-C_6 alkyl), or C_1-C_6 alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

33. A compound according to claim 29, wherein

R_5 is either



wherein

Z_1 is H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, or C_1-C_4 alkoxy; and

Z_2 is C_1-C_4 alkyl, -$C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, -NR_6R_7, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, C_1-C_6 alkoxycarbonyl, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, or -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$;

Z_3 is H, C_1-C_4 alkyl, -$C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, -NR_6R_7, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, C_1-C_6 alkoxycarbonyl, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, or -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$;

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

R_{15} is H or C_1-C_6 alkyl;

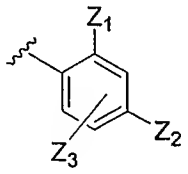
R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17}, and the nitrogen to which they are attached form a morpholinyl ring;

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

34. A compound according to claim 33, wherein

R_5 is of the formula:



Z_1 is H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, or C_1-C_4 alkoxy; and

Z_2 is C_1-C_4 alkyl, $-C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, $-NR_6R_7$, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, C_1-C_6 alkoxycarbonyl, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, or -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$;

Z_3 is H, C_1-C_4 alkyl, $-C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, $-NR_6R_7$, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, C_1-C_6 alkoxycarbonyl, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, or -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$;

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

R_{15} is H or C_1-C_6 alkyl;

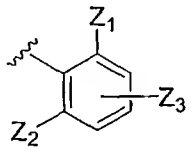
R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17}, and the nitrogen to which they are attached form a morpholinyl ring;

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

35. A compound according to claim 33, wherein

R_5 is of the formula:



wherein

Z_1 is H, halogen, C_1-C_4 alkyl C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, or C_1-C_4 alkoxy; and

Z_2 is C_1-C_4 alkyl, $-C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, $-NR_6R_7$, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, C_1-C_6 alkoxycarbonyl, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, or -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$;

Z_3 is H, C_1-C_4 alkyl, $-C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, $-NR_6R_7$, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, C_1-C_6 alkoxycarbonyl, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, or -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$;

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

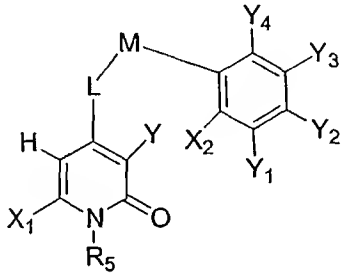
R_{15} is H or C_1-C_6 alkyl;

R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17}, and the nitrogen to which they are attached form a morpholinyl ring;

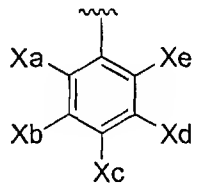
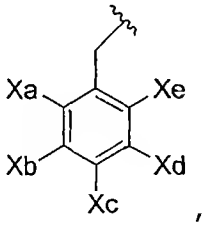
R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

36. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

L and M are indepedently selected from -O-, -CH_2-, -S-,-NR-, -N(R)-N(R)-, C(=O)-, -SO_2-;

R_5 is  or  , wherein

X_1, X_2, X_a, X_b, X_c, X_d, and X_e at are independently selected from -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, -NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, heteroaryl, heterocycloalkyl, C_3-C_7 cycloalkyl, R_6R_7N-(C_1-C_6 alkyl)-, -CO_2-(C_1-C_6)alkyl, -N(R)C(O)NR_6R_7, -N(R)C(O)-(C_1-C_6)alkoxy, CO_2R-(C_1-C_6 alkyl)-, or -$SO_2NR_6R_7$; wherein the heteroaryl and heterocycloalkyl groups are optionally substituted with -NR_6R_7, -C(O)NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halogen; or

R_5 is heteroaryl or heteroarylalkyl, wherein the heteroaryl and heteroaryl groups are optionally substituted with 1,2, 3, or 4 groups that are independently $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-CO_2-(C_1-C_6)$alkyl, $-N(R)C(O)NR_6R_7$, or $-N(R)C(O)-(C_1-C_6)$alkoxy; wherein

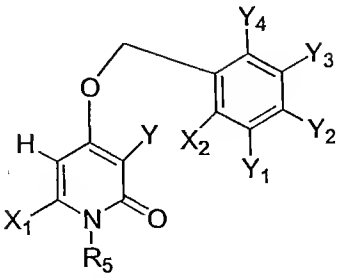
R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_6 thiohydroxyalkyl, $-(C_1-C_4)$alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), $-O-C_1-C_4$ alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

R at each occurrence is independently H or C_1-C_6 alkyl; and

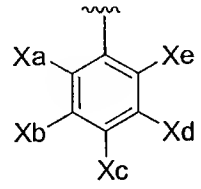
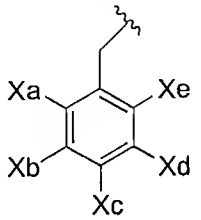
Y, Y_1, Y_2, Y_3, and Y_4 are independently selected from H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, alkenyl, alkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, and carboxyl.

37. A compound according to claim 36 of the formula



or a pharmaceutically acceptable salt thereof.

38. A compound according to claim 37, wherein

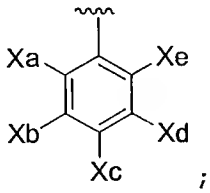
R_5 is  or  .

39. A compound according to claim 31, wherein

Y_2, Y_4, and Y are independently halogen; and

Y_1 and Y_3 are both hydrogen.

40. A compound according to claim 39, wherein

R_5 is  ;

X_1 and X_2 are independently H, methyl, NR_6R_7, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, -$C(O)NR_6R_7$, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, or -(C_1-C_4 alkyl)-morpholinyl; and

X_a and X_e are independently halogen, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), methyl, or hydrogen.

41. A compound according to claim 40, wherein

one of X_b and X_c is hydrogen and the other is $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-SO_2NR_6R_7$, or halogen; where

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, $-(C_1-C_4)$alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), $-O-C_1-C_4$ alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

42. A compound according to claim 41, wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, $-(C_1-C_4)$alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, NH_2, NH(alkyl),

N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3.

43. A compound according to claim 42, wherein

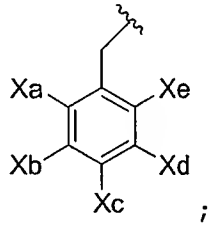
X_a is hydrogen, methyl, fluorine, or chlorine;

X_c and X_d are both hydrogen;

X_b is $-NR_6R_7$, $-(C_1$-C_4 alkyl$)$-$C(O)NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, -$C(O)NR_6R_7$; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, or C_1-C_6 alkanoyl, wherein each of the above is optionally substituted with 1, 2, or 3 groups that are independently OH, SH, halogen, or C_3-C_6 cycloalkyl.

44. A compound according to claim 39, wherein

R_5 is 

;

X_a is H, fluoro, chloro, or methyl;

X_e is hydrogen, halogen, or methyl; and

X_b is H;

X_d is H or halogen;

45. A compound according to claim 44, wherein

X_c is $-SO_2NR_6R_7$, or halogen; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, -(C_1-C_4)alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or

phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen; or

X_c is fluoro, chloro, $-NH_2$, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), $-SO_2NH_2$, $-SO_2$NH(C_1-C_6 alkyl), $-SO_2$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), or piperazinyl, wherein the piperazinyl group is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

46. A compound according to claim 44, wherein

X_c is $-C(O)NR_6R_7$, -(C_1-C_6 alkyl)-$C(O)NR_6R_7$, $-NR_6R_7$, or R_6R_7N-(C_1-C_6 alkyl)-; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 dihydroxyalkyl, -(C_1-C_4)alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are

independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, $-NH_2$, -NH(alkyl), -N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

47. A compound according to claim 46, wherein

R_6 is hydrogen; and

R_7 is C_1-C_6 alkyl or C_1-C_6 alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), OH, SH, cyclopropyl, or C_1-C_4 alkoxy;

48. A compound according to claim 47, wherein

X_c is $-C(O)NR_6R_7$.

49. A compound according to claim 47, wherein

X_c is NR_6R_7, or R_6R_7N-(C_1-C_6 alkyl)-.

50. A compound according to claim 38, wherein

X_a is hydrogen;

two of X_b, X_c, and X_d are hydrogen and the other is $-C(O)NR_6R_7$, -(C_1-C_6 alkyl)-$C(O)NR_6R_7$, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)- or -CO_2-(C_1-C_6)alkyl; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6

dihydroxyalkyl, -(C_1-C_4)alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen; and

X_e is hydrogen, methyl, C_1-C_2 alkoxy, or halogen.

51. A compound according to claim 50, wherein

X_b is $-C(O)NR_6R_7$, -(C_1-C_6 alkyl)-$C(O)NR_6R_7$, $-NR_6R_7$, or R_6R_7N-(C_1-C_6 alkyl)- wherein

R_6 is hydrogen or C_1-C_4 alkyl;

R_7 is OH, C_1-C_6 alkyl or C_1-C_6 alkanoyl, wherein the alkyl and alkanoyl groups substituted with 1, 2, or 3 groups that are independently NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), C_3-C_6 cycloalkyl, OH, or C_1-C_4 alkoxy.

52. A compound according to claim 38, wherein

X_a is halogen or methyl;

X_b is H, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, $-C(O)NR_6R_7$, or $-CO_2$-(C_1-C_6)alkyl;

X_c is $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, $-C(O)NR_6R_7$, halogen, $-CO_2$-(C_1-C_6)alkyl, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), $-SO_2NH_2$, $-SO_2NH$(C_1-C_6 alkyl), $-SO_2N$(C_1-C_6 alkyl)(C_1-C_6

alkyl), or piperazinyl, wherein the piperazinyl group is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

X_d is hydrogen;

X_e is H, methyl, NH_2, $NH(C_1$-C_6 alkyl) or $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl).

53. A compound according to claim 38, wherein

X_1, X_2, X_a, X_b, X_c, X_d, and X_e are independently selected from H, OH, halogen, CF_3, alkyl, OCF_3, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, thienyl, furyl, pyrrolyl, piperidinyl, piperazinyl, or C_3-C_7 cycloalkyl, wherein each of the above is optionally substituted with $-NR_6R_7$, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)$-C(O)NR_6R_7$, $R_6R_7N-(C_1$-C_6 alkyl)-, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halogen.

54. A compound according to claim 37, wherein

R_5 is a heteroaryl or heteroarylalkyl group, where each heteroaryl is pyrazolyl, imidazolyl, furanyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, imidazolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, dihydroisoquinolinyl, or indolyl, each of which is optionally substituted with 1, 2, 3, or 4 groups that are independently $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)$-C(O)NR_6R_7$, $-NR_6R_7$, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, hydrogen, hydroxy, halogen, haloalkyl, alkyl, haloalkoxy, $R_6R_7N-(C_1$-C_6 alkyl)-, $-CO_2-(C_1$-C_6)alkyl, $-N(R)C(O)NR_6R_7$, or $-N(R)C(O)-(C_1$-C_6)alkoxy; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6

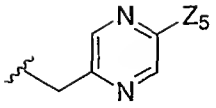
dihydroxyalkyl, C_1-C_6 thiohydroxyalkyl, -(C_1-C_4)alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF.

55. A compound according to claim 54, wherein
Y_2, Y_4, and Y are independently halogen; and
Y_1 and Y_3 are both hydrogen.

56. A compound according to claim 55, wherein
X_1 and X_2 are independently H, methyl, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, or -(C_1-C_4 alkyl)-morpholinyl.

57. A compound according to claim 56, wherein
R_5 is pyridyl C_1-C_6 alkyl, pyrimidinyl C_1-C_6 alkyl, or pyrazinyl C_1-C_6 alkyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -C(O)NR_6R_7.

58. A compound according to claim 57, wherein
R_5 is of the formula:



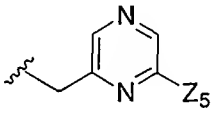
wherein

Z_5 is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-C(O)NR_6R_7, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

59. A compound according to claim 57, wherein

R_5 is of the formula:

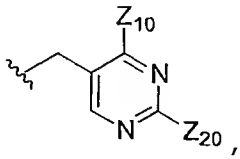


wherein

Z_5 is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-C(O)NR_6R_7, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

60. A compound according to claim 57, wherein

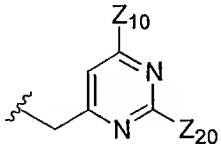
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is -(C_1-C_4 alkyl)-C(O)NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

61. A compound according to claim 57, wherein

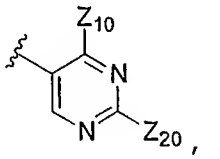
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is -(C_1-C_4 alkyl)-C(O)NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

62. A compound according to claim 57, wherein

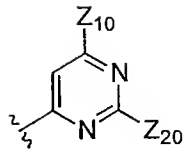
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is -(C_1-C_4 alkyl)-C(O)NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

63. A compound according to claim 57, wherein

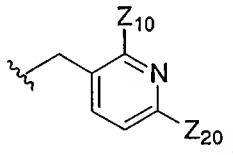
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is -(C_1-C_4 alkyl)-C(O)NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

64. A compound according to claim 57, wherein

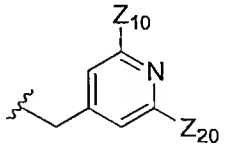
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is -(C_1-C_4 alkyl)-C(O)NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

65. A compound according to claim 57, wherein

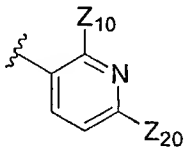
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is -(C_1-C_4 alkyl)-C(O)NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

66. A compound according to claim 57, wherein

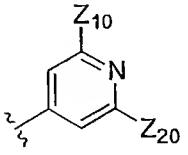
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is -(C_1-C_4 alkyl)-C(O)NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

67. A compound according to claim 57, wherein

R_5 is of the formula:  , wherein

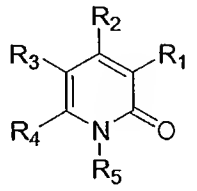
Z_{10} is H or methyl; and

Z_{20} is -(C_1-C_4 alkyl)-C(O)NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups

that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

68. A method of treating a TNF mediated disorder, a p38 kinase mediated disorder, inflammation and/or arthritis in a subject, the method comprising treating a subject having or susceptible to such disorder or condition with a compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein

R_1 is H, halogen, NO_2, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, -CN, aryl, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN, haloalkyl, haloalkoxy or CO_2R;

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, or C_3-C_7 cycloalkyl;

R_2 is H, OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthio, arylthioalkoxy, arylalkynyl, alkoxy, aryloxy(C_1-C_6)alkyl, alkyl, alkynyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N$(alkyl)$(CH_2)_n$aryl, alkoxyalkoxy, dialkylamino, alkyl, alkoxy, aryl, arylalkyl, heteroaryl,

heteroarylalkyl, arylalkenyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxyalkoxy, NR_8R_9, dialkylamino, or CO_2R, wherein

n is 0, 1, 2, 3, 4, 5 or 6;

each of which groups is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-(C_1-C_6)$alkyl-$N(R)-CO_2R_{30}$, haloalkyl, heteroaryl, heteroarylalkyl, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-NRC(O)NR_{16}R_{17}$, haloalkoxy, alkyl, CN, alkoxy, alkoxycarbonyl, phenyl, $-SO_2$-phenyl wherein the phenyl and $-SO_2$-phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or NO_2, or $-OC(O)NR_6R_7$, wherein

R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17} and the nitrogen to which they are attached form a morpholinyl ring;

R_6 and R_7 are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkanoyl, arylalkyl, arylalkoxy, alkoxycarbonyl, $-SO_2$-alkyl, OH, alkoxy, alkoxyalkyl, arylalkoxycarbonyl, $-(C_1-C_4)$alkyl-CO_2-alkyl, heteroarylalkyl, or arylalkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, heterocycloalkyl, heterocycloalkylalkyl, C_3-C_7 cycloalkyl, alkoxy, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-alkanoyl, alkyl, haloalkyl, carboxaldehyde, or haloalkoxy; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, pyrrolidinyl, thiomorpholinyl, thiomorpholinyl S-oxide,

thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, alkoxycarbonyl, C_1-C_4 alkoxy, hydroxyl, hydroxyalkyl, dihydroxyalkyl, or halogen;

R at each occurrence is independently hydrogen or C_1-C_6 alkyl optionally substituted with optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

R_{30} is C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

each R_8 is independently hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl;

each R_9 is hydrogen, alkyl, alkanoyl, arylalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, arylalkanoyl, -SO_2-phenyl, and aryl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl;

R_3 is H, halogen, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, -OC(O)NH$(CH_2)_n$aryl, arylalkoxy, -OC(O)N(alkyl)$(CH_2)_n$aryl, aryloxy, arylthio,

thioalkoxy, arylthioalkoxy, alkenyl, $-NR_6R_7$, $NR_6R_7-(C_1-C_6)$alkyl, or alkyl, wherein

the aryl portion of arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, $-OC(O)NH(CH_2)_n$aryl, arylalkoxy, $-OC(O)N(alkyl)(CH_2)_n$aryl, and arylthioalkoxy, is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, haloalkyl, or haloalkoxy,

wherein n is 0, 1, 2, 3, 4, 5, or 6; or

R_4 is hydrogen or R_4 is alkyl unsubstituted or substituted with one or two groups that are independently CO_2R, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, arylalkoxy, arylalkyl, heteroaryl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-NR_6R_7$, alkoxy, carboxaldehyde, CO_2R, alkoxyalkyl, or alkoxyalkoxy, wherein the aryl portion of arylalkoxy and arylalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy; and

R_5 is H, aryl, arylalkyl, arylthioalkyl, alkyl optionally substituted with 1, 2, or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, C_3-C_7 cycloalkyl, or alkanoyl, alkoxy, alkoxyalkyl optionally substituted with one trimethylsilyl group, amino, alkoxycarbonyl, hydroxyalkyl, dihydroxyalkyl, alkynyl, $-SO_2$-alkyl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -alkyl-S-aryl, -alkyl-SO_2-aryl, heteroarylalkyl, heterocycloalkyl, heteroaryl, or alkenyl optionally substituted with alkoxycarbonyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, CO_2R, CN, OH, hydroxyalkyl, dihydroxyalkyl, amidinooxime, $-NR_6R_7$, $-NR_8R_9$, $R_6R_7N-(C_1-C_6$ alkyl)-, carboxaldehyde, SO_2alkyl, $-SO_2H$, $-SO_2NR_6R_7$, alkanoyl wherein the alkyl portion is optionally substituted with OH, halogen or alkoxy, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, amidino, haloalkyl, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)NR_{16}R_{17}$, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, or haloalkoxy; wherein

R_{15} is H or C_1-C_6 alkyl;

R_{18} is C_1-C_6 alkyl optionally substituted with $-O-(C_2-C_6$ alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

69. A method according to claim 68 for treating or preventing inflammation; arthritis, rheumatoid arthritis, spondylarthropathies, gouty arthritis, osteoarthritis, systemic lupus erthematosus, juvenile arthritis; neuroinflammation; pain, neuropathic pain; fever; pulmonary disorders, lung inflammation, adult respiratory distress syndrome, pulmonary sarcoisosis, asthma, silicosis, chronic pulmonary inflammatory disease; cardiovascular disease, arteriosclerosis, myocardial infarction, thrombosis, congestive heart failure, cardiac reperfusion injury; cardiomyopathy; reperfusion injury; renal reperfusion injury; ischemia including stroke and brain ischemia; brain trauma; brain edema; liver disease and nephritis; gastrointestinal conditions, inflammatory bowel disease, Crohn's disease,

gastritis, irritable bowel syndrome, ulcerative colitis; ulceratiuve diseases, gastric ulcers; ophthalmic diseases, retinitis, retinopathies, uveitis, ocular photophobia, acute injury to the eye tissue; ophthalmological conditions, corneal graft rejection, ocular neovascularization, retinal neovascularization, neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasias, neovascular glaucoma; diabetes; diabetic nephropathy; skin-related conditions, psoriasis, eczema, burns, dermatitis, keloid formation, scar tissue formation, angiogenic disorders; viral and bacterial infections, sepsis, septic shock, gram negative sepsis, malaria, meningitis, opportunistic infections, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, herpes virus; myalgias due to infection; influenza; endotoxic shock; toxic shock syndrome; autoimmune disease, graft vs. host reaction and allograft rejections; treatment of bone resorption diseases, osteoporosis; multiple sclerosis; disorders of the female reproductive system, endometriosis; hemaginomas, infantile hemagionmas, angiofibroma of the nasopharynx, avascular necrosis of bone; benign and malignant tumors/neoplasia, cancer, colorectal cancer, brain cancer, bone cancer, epithelial call-derived neoplasia (epithelial carcinoma), basal cell carcinoma, adenocarcinoma, gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, skin cancer, squamus cell and/or basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that affect epithelial cells throughout the body; leukemia; lymphoma; systemic lupus erthrematosis (SLE); angiogenesis including neoplasia;

metastasis; central nervous system disorders, central nervous system disorders having an inflammatory or apoptotic component, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, canine B-cell lymphoma, and peripheral neuropathy.

70. A compound according to claim 1, which is

1-benzyl-4-(benzyloxy)-3-bromopyridin-2(1*H*)-one;

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(4-fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one;

4-bromo-2-(2,6-dichlorophenyl)-5-[(2,4-difluorobenzyl)oxy]pyridazin-3(2*H*)-one;

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-[(3-methylbenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3-bromo-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(4-methylbenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(4-chlorobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-methoxybenzyl)pyridin-2(1*H*)-one;

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoic acid;

4-(benzyloxy)-3-bromo-1-(2-fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[4-(methylthio)benzyl]pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3-chloropyridin-2(1*H*)-one;

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}-*N*'-hydroxybenzenecarboximidamide;

methyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoate;

3-bromo-4-[(3-chlorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile;

4-(benzyloxy)-3-bromo-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(4-bromobenzyl)pyridin-2(1*H*)-one;

4-{[3-bromo-4-[(4-fluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile;

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1*H*)-one;

4-bromo-2-(2,6-dichlorophenyl)-5-{[2-(hydroxymethyl)benzyl]oxy}pyridazin-3(2*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-1-(2,4-difluorobenzyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1*H*)-one; or a pharmaceutically acceptable salt thereof.

71. A compound according to claim 1, which is

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-fluorobenzyl)pyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(4-chlorobenzyl)-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-4-[(4-chlorobenzyl)oxy]-1-[2-(phenylthio)ethyl]pyridin-2(1*H*)-one;

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(2-phenylethyl)pyridin-2(1*H*)-one;

3-bromo-4-hydroxy-1-(4-hydroxybenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(piperidin-3-ylmethyl)pyridin-2(1*H*)-one hydrochloride;

3-bromo-1-(4-methoxybenzyl)-4-phenoxypyridin-2(1*H*)-one;

1-benzyl-2-oxo-4-phenoxy-1,2-dihydropyridine-3-carbaldehyde;

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(3-phenylpropyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-1-[4-(benzyloxy)benzyl]-3-bromopyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[3-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(piperidin-4-ylmethyl)pyridin-2(1*H*)-one hydrochloride;

1-benzyl-4-(benzylthio)-3-bromopyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one;

1-benzyl-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3-(hydroxymethyl)pyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one;

4-(benzyloxy)-1-(4-bromobenzyl)pyridin-2(1*H*)-one;

3-bromo-1-(4-methylbenzyl)-4-[(4-methylbenzyl)oxy]pyridin-2(1*H*)-one;

methyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoate;

4-(benzyloxy)-3-bromo-1-(2-thien-3-ylethyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(2-thien-2-ylethyl)pyridin-2(1*H*)-one;

1-benzyl-4-[(3-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-1-(2-fluorobenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one hydrobromide;

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one;

3-bromo-1-(3-chlorobenzyl)-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(3-chlorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

4-(benzyloxy)-1-(4-chlorobenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(4-*tert*-butylbenzyl)pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-6-methylpyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3,5-dibromo-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one;

1-benzyl-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

1-(2-bromobenzyl)-3-[(2-bromobenzyl)oxy]pyridin-2(1*H*)-one;

methyl 5-chloro-1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate;

3-benzyl-4-hydroxy-1-(2-phenylethyl)pyridin-2(1*H*)-one;

5-bromo-1-(2-chloro-6-fluorobenzyl)-3-methylpyridin-2(1*H*)-one;

1-(2-bromobenzyl)-3-[(2-bromobenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3-bromopyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-2-oxo-1,2-dihydropyridine-3-carbaldehyde;

1-benzyl-4-chloro-2-oxo-1,2-dihydropyridine-3-carbaldehyde;

1-benzyl-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carbaldehyde;

1-benzyl-4-(benzyloxy)-3-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-1-(4-fluorobenzyl)pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3,5-dibromopyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[4-(methylthio)benzyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(4-fluorobenzyl)pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3-chloropyridin-2(1*H*)-one;

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate;

1-benzyl-3-bromo-4-(2-phenylethyl)pyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-(3-phenylpropyl)pyridin-2(1*H*)-one;

1-benzyl-3-methyl-4-(2-phenylethyl)pyridin-2(1*H*)-one;

1-benzyl-3-methyl-4-(3-phenylpropyl)pyridin-2(1*H*)-one;

1-benzyl-4-(benzylthio)-3-methylpyridin-2(1*H*)-one;

1-benzyl-4-(benzylthio)-3-bromopyridin-2(1*H*)-one;

(product) 1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methanesulfonate;

3-acetyl-4-hydroxy-6-methyl-1-[choro]phenylpyridin-2(1*H*)-one;

6-(benzyloxy)-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile;

3-benzoyl-6-(benzyloxy)-1-methylpyridin-2(1*H*)-one;

3-benzyl-6-(benzyloxy)-1-methylpyridin-2(1*H*)-one;

1-benzyl-4-hydroxypyridin-2(1*H*)-one;

1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methanesulfonate;

1-benzyl-4-(benzylthio)pyridin-2(1*H*)-one

1-benzyl-4-(benzylthio)-3-bromopyridin-2(1*H*)-one;

4-amino-1-benzylpyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)pyridin-2(1*H*)-one;

1-benzyl-4-hydroxypyridin-2(1*H*)-one;

1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate;

or a pharmaceutically acceptable thereof.

72. A compound according to claim 1, which is

4-(benzyloxy)-1-(4-methylbenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromopyridin-2(1*H*)-one;

methyl 4-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl} benzoate;

methyl-4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl} benzoate;

4-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl} benzonitrile;

4-(benzyloxy)-1-(4-*tert*-butylbenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethyl) benzyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[3-(trifluoromethyl) benzyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl) benzyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy) benzyl]pyridin-2(1*H*)-one;

1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one;

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate;

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1H)-one;

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate;

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1H)-one;

1-Benzyl-4-[2,6-(dichlorobenzyl)oxy]pyridin-2(1H)-one;

4-[(2,6-dichlororbenzyl)oxy]pyridine-1-oxide;

4-[(2,6-dichlorobenzyl)oxy]pyridine 1-oxide;

1-Benzyl-3-bromo-4-[2,6-(dichlorobenzyl)oxy]pyridin-2(1H)-one;

1-Benzyl-3-bromo-4-[(4-methylbenzyl)oxy]pyridin-2(1H)-one;

1-Benzyl-4-[benzylthio]-3-bromopyridin-2(1H)-one;

1-benzyl-4-(benzyloxy)-3-iodopyridin-2(1H)-one;

1-benzyl-4-(benzyloxy)-3-vinylpyridin-2(1H)-one;

1-benzyl-4-(benzyloxy)-3-ethylpyridin-2(1H)-one;

3-acetyl-4-(benzyloxy)-1-(2-chlorophenyl)-6-methylpyridin-2(1H)-one;

3-acetyl-1-(2-chlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one;

1-benzyl-3-bromo-4-hydroxypyridin-2(1H)-one;

1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate;

1-benzyl-3-bromo-4-(phenylethynyl)pyridin-2(1H)-one;

3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1H)-one;

1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one;

3-bromo-1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one;

3-bromo-1-(3-fluorobenzyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate;

3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(phenylethynyl)pyridin-2(1H)-one;

3-acetyl-1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one;

1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one;

4-(benzyloxy)-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1H)-one;

3-bromo-1-(3-fluorobenzyl)-4-(2-phenylethyl)pyridin-2(1H)-one;

3-bromo-1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one;

3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate;

3-bromo-1-(3-fluorobenzyl)-4-(phenylethynyl)pyridin-2(1H)-one;

4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1H)-one;

4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one;

4-(benzyloxy)-1-(3-fluorobenzyl)-3-[(trimethylsilyl)ethynyl]pyridin-2(1H)-one;

4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one;

1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one;

4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one;

or a pharmaceutically acceptable salt thereof.

73. A compound according to claim 1, which is

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-methoxybenzyl)pyridin-2(1*H*)-one;

3-bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(3-chlorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

4-{[3-bromo-4-[(4-fluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile;

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-1-(2,4-difluorobenzyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-[(3-methylbenzyl)oxy]piperidin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1*H*)-one;

or a pharmaceutically acceptable salt thereof.

74 . A compound according to claim 1, which is

1-(1-acetyl-2,3-dihydro-1*H*-indol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-2,3-dihydro-1*H*-indol-5-yl)-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-2,3-dihydro-1*H*-indol-5-yl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one;

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]indoline-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-2,3-dihydro-1*H*-indol-5-yl]pyridin-2(1*H*)-one;

1-(1-acetyl-1*H*-indol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-indol-5-yl)-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-indol-5-yl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one;

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-indole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-indol-5-yl]pyridin-2(1*H*)-one;

1-(2-acetyl-2,3-dihydro-1*H*-isoindol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2-glycoloyl-2,3-dihydro-1*H*-isoindol-5-yl)-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(*N*-methylglycyl)-2,3-dihydro-1*H*-isoindol-5-yl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]-6-methylpyridin-2(1*H*)-one;

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

oxopyridin-1(2*H*)-yl]-1,3-dihydro-2*H*-isoindole-2-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(methylsulfonyl)-2,3-dihydro-1*H*-isoindol-5-yl]pyridin-2(1*H*)-one;

1-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(*N*-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-6-methylpyridin-2(1*H*)-one;

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3,4-dihydroisoquinoline-2(1*H*)-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]pyridin-2(1*H*)-one;

1-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-6-

methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(*N*-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-6-methylpyridin-2(1*H*)-one;

7-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3,4-dihydroisoquinoline-2(1*H*)-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]pyridin-2(1*H*)-one;

1-(1-acetyl-1*H*-benzimidazol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-benzimidazol-5-yl)-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-benzimidazol-5-yl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

oxopyridin-1(2*H*)-yl]-1*H*-benzimidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-benzimidazol-5-yl]pyridin-2(1*H*)-one;

3-chloro-1-(1,3-diacetyl-2,3-dihydro-1*H*-benzimidazol-5-yl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-(3-acetyl-1-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-[3-acetyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-[3-acetyl-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-[3-acetyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-[3-acetyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-acetyl-5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

1-(1-acetyl-3-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1,3-diglycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(*N*-

methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-glycoloyl-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

1-[1-acetyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

1-[1,3-bis(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(2-hydroxy-2-methylpropanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(2-hydroxy-2-methylpropanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(2-hydroxy-2-methylpropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

1-[1-acetyl-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

1-[1,3-bis(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(*N*-methylglycyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]pyridin-2(1*H*)-one;

1-[1-acetyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-

methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxypropanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

1-[1,3-bis(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxypropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

1-[1-acetyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxy-3-methylbutanoyl)-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxy-3-

methylbutanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxy-3-methylbutanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

1-[1,3-bis(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxy-3-methylbutanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-acetyl-6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-glycoloyl-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-benzimidazole-1,3(2*H*)-dicarboxamide;

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

1-[1-acetyl-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one;

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

1-[1,3-bis(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-[3-acetyl-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-(1-acetyl-1*H*-pyrrol-3-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-pyrrol-3-yl)-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-pyrrol-3-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-pyrrol-3-yl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-pyrrol-3-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-pyrrol-3-yl]-6-methylpyridin-2(1*H*)-one;

3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-pyrrole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-pyrrol-3-yl]pyridin-2(1*H*)-one;

1-(1-acetyl-1*H*-imidazol-4-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-imidazol-4-yl)-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-imidazol-4-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-imidazol-4-yl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-imidazol-4-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-imidazol-4-yl]-6-methylpyridin-2(1*H*)-one;

4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-imidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-imidazol-4-yl]pyridin-2(1*H*)-one;

1-(1-acetyl-1*H*-pyrazol-4-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-pyrazol-4-yl)-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-pyrazol-4-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-pyrazol-4-yl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-pyrazol-4-yl]-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-pyrazol-4-yl]-6-methylpyridin-2(1*H*)-one;

4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-pyrazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-pyrazol-4-yl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-isoquinolin-7-yl-6-methylpyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(isoquinolin-6-ylmethyl)pyridin-2(1*H*)-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-indol-2-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,3-dihydro-1*H*-indol-5-ylmethyl)pyridin-2(1*H*)-one;

1-[(1-acetyl-2,3-dihydro-1*H*-indol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1-glycoloyl-2,3-dihydro-1*H*-indol-5-yl)methyl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(*N*-

methylglycyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}indoline-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(methylsulfonyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,3-dihydro-1*H*-isoindol-5-ylmethyl)pyridin-2(1*H*)-one;

1-[(2-acetyl-2,3-dihydro-1*H*-isoindol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(2-glycoloyl-2,3-dihydro-1*H*-isoindol-5-yl)methyl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(*N*-methylglycyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-

1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-isoindole-2-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(methylsulfonyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1,2,3,4-tetrahydroisoquinolin-6-ylmethyl)pyridin-2(1*H*)-one;

1-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(*N*-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3,4-dihydroisoquinoline-2(1*H*)-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1,2,3,4-tetrahydroisoquinolin-5-ylmethyl)pyridin-2(1*H*)-one;

1-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(2-glycoloyl-

1,2,3,4-tetrahydroisoquinolin-5-yl)methyl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(*N*-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3,4-dihydroisoquinoline-2(1*H*)-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,3-dihydro-1*H*-benzimidazol-5-ylmethyl)pyridin-2(1*H*)-one;

1-[(1-acetyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-

yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

1-[(3-acetyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-1-[(1,3-diacetyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

1-[(3-acetyl-1-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

1-{[3-acetyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

1-{[3-acetyl-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

1-{[3-acetyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

1-{[3-acetyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

1-{[3-acetyl-1-(methylsulfonyl)-2,3-dihydro-1*H*-

benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(3-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]pyridin-2(1*H*)-one;

1-[(1-acetyl-3-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1,3-diglycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

1-{[1-acetyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-

difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

1-{[1,3-bis(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(2-hydroxy-2-methylpropanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(2-hydroxy-2-methylpropanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(2-hydroxy-2-methylpropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

1-{[1-acetyl-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-

methylpropanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

1-{[1,3-bis(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxypropanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(*N*-methylglycyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

1-{[1-acetyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxypropanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

1-{[1,3-bis(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxypropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

1-{[1-acetyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-

1*H*-benzimidazole-1-carboxamide;

1-{[1,3-bis(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-acetyl-6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1*H*-benzimidazole-1,3(2*H*)-dicarboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

1-{[1-acetyl-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(*N*-methylglycyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxypropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

1-{[1,3-bis(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-benzimidazol-2-one;

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-

1(2*H*)-yl]methyl}-1-glycoloyl-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

1-acetyl-6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-benzimidazol-2-one;

1,3-diacetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-benzimidazol-2-one;

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-1,3-dihydro-2*H*-benzimidazol-2-one;

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-

benzimidazol-2-one;

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-1,3-dihydro-2*H*-benzimidazol-2-one;

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-diglycoloyl-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-

1(2*H*)-yl]methyl}-3-glycoloyl-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-3-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-

benzimidazol-2-one;

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-3-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-3-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-

1(2*H*)-yl]methyl}-1-glycoloyl-3-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

3-acetyl-6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-1*H*-benzimidazole-1,3(2*H*)-dicarboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(*N*-methylglycyl)-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one;

3-benzyl-4-hydroxy-1-(2-phenylethyl)pyridin-2(1*H*)-one;

1-benzyl-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carbaldehyde;

1-benzyl-4-chloro-2-oxo-1,2-dihydropyridine-3-carbaldehyde;

methyl 5-chloro-1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate;

5-bromo-1-(2-chloro-6-fluorobenzyl)-3-methylpyridin-2(1*H*)-one;

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorophenyl)ethynyl]-6-methylpyridin-2(1*H*)-one;

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorophenyl)ethynyl]-6-methylpyridin-2(1*H*)-one;

methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoate;

4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile;

4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1*H*)-one;

4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1*H*)-one;

3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzaldehyde;

4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1*H*)-one;

4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1*H*)-one;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoic acid;

4-[(2,4-difluorobenzyl)oxy]-1-[4-(dimethylamino)-2,6-difluorophenyl]-6-methylpyridin-2(1*H*)-one;

4-[(2,4-difluorobenzyl)oxy]-1-{2,6-difluoro-4-[(2-hydroxyethyl)(methyl)amino]phenyl}-6-methylpyridin-2(1*H*)-one;

methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoate;

3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoic acid;

4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1*H*)-one;

3-bromo-1-{[5-(chloromethyl)pyrazin-2-yl]methyl}-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(hydroxymethyl)-2-methoxyphenyl]-6-methylpyridin-2(1*H*)-one;

methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoate;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyridin-2(1*H*)-one;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-[2-(dimethylamino)ethyl]benzamide;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-methoxyethyl)benzamide;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-[2-(dimethylamino)ethyl]-*N*-methylbenzamide;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)-*N*-methylbenzamide;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-methoxyethyl)-*N*-methylbenzamide;

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide;

methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-fluorobenzoate;

4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-methylbenzoic acid;

1-(4-bromo-2-methylphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-[(1-acetyl-1*H*-indol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1*H*)-one;

methyl 2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-3,5-difluorobenzylcarbamate;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one;

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*,*N*-dimethylbenzamide;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)-4-methylbenzamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{4-[(4-methylpiperazin-1-yl)carbonyl]benzyl}pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1*H*-indol-5-ylmethyl)pyridin-2(1*H*)-one;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-methylbenzamide;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-methoxyethyl)-4-methylbenzamide;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,4-dimethylbenzamide;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*,4-trimethylbenzamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-methyl-5-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(1-hydroxy-1-methylethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one;

1-(2-bromobenzyl)-3-[(2-bromobenzyl)oxy]pyridin-2(1*H*)-one;

1-(2-bromobenzyl)-3-[(2-bromobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(4-methoxybenzyl)-4-phenoxypyridin-2(1*H*)-one;

1-benzyl-2-oxo-4-phenoxy-1,2-dihydropyridine-3-carbaldehyde;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-dimethylaminomethyl-benzyl)-6-methyl-1H-pyridin-2-one;

N-{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-2-hydroxy-acetamide;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[4-(piperidine-1-carbonyl)-benzyl]-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(ethoxyamino)methyl]pyridin-2(1*H*)-one;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-

pyridin-1-ylmethyl]-N-isopropyl-benzamide;

N-(3-aminopropyl)-4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide hydrochloride;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,4-dimethylbenzamide;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N,N-bis-(2-hydroxy-ethyl)-benzamide;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[4-(pyrrolidine-1-carbonyl)-benzyl]-1H-pyridin-2-one;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-hydroxy-benzamide;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-methyl-benzamide;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-dimethylamino-ethyl)-benzamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(1*H*-indazol-5-ylmethyl)pyridin-2(1*H*)-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-benzyl]-1H-pyridin-2-one;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzaldehyde;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-dimethylaminomethyl-benzyl)-6-methyl-1H-pyridin-2-one;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-methoxyethyl)-4-methylbenzamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-(dimethylamino)-4,6-difluorophenyl]-6-methylpyridin-2(1*H*)-one hydrochloride;

N-(2-aminoethyl)-4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide hydrochloride;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-hydroxy-ethyl)-benzamide;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-hydroxymethyl-benzyl)-6-methyl-1H-pyridin-2-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-(dimethylamino)-4,6-difluorophenyl]-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1*H*)-one;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-methoxy-ethyl)-benzamide;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-{4-[(2-hydroxy-ethylamino)-methyl]-benzyl}-6-methyl-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(dimethylamino)methyl]pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-methyl-5-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(4-methylaminomethyl-benzyl)-1H-pyridin-2-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[4-(morpholine-4-carbonyl)-benzyl]-1H-pyridin-2-one;

N-(2-aminoethyl)-3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide;

N-(3-aminopropyl)-3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide hydrochloride;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-methoxy-ethyl)-N-methyl-benzamide;

1-(4-Aminomethyl-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1*H*)-one hydrochloride;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[4-(isopropylamino-

methyl)-benzyl]-6-methyl-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1*H*)-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-{3-[(2-hydroxy-ethylamino)-methyl]-benzyl}-6-methyl-1H-pyridin-2-one;

1-(3-Aminomethyl-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-hydroxy-benzyl)-6-methyl-1H-pyridin-2-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(dimethylamino)methyl]pyridin-2(1*H*)-one;

N-{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-acetamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2,6-difluoro-4-[(2-hydroxyethyl)(methyl)amino]phenyl}-6-methylpyridin-2(1*H*)-one;

ethyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoate;

1-[3-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one trifluoroacetate;

1-(3-{[Bis-(2-hydroxy-ethyl)-amino]-methyl}-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[3-(isopropylamino-methyl)-benzyl]-6-methyl-1H-pyridin-2-one;

{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-carbamic acid tert-butyl ester;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-6-methyl-1H-pyridin-2-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-dimethylaminomethyl-benzyl)-1H-pyridin-2-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(3-piperidin-1-ylmethyl-benzyl)-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-{[(2-methoxyethyl)amino]methyl}pyridin-2(1*H*)-one;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-methylbenzamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2,4-difluoro-6-[(2-hydroxyethyl)(methyl)amino]phenyl}-6-methylpyridin-2(1*H*)-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(3-morpholin-4-ylmethyl-benzyl)-1H-pyridin-2-one;

3-bromo-1-(2,6-dimethylphenyl)-6-methyl-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(2,6-dimethylphenyl)-6-methyl-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1*H*)-one;

1-(4-{[Bis-(2-hydroxy-ethyl)-amino]-methyl}-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1*H*)-one;

4-Benzyloxy-3-bromo-1-(4-fluoro-benzyl)-1H-pyridin-2-one;

4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzamide;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*,4-trimethylbenzamide;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-isopropylbenzamide;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzamide;

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzonitrile;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(3-

piperazin-1-ylmethyl-benzyl)-1H-pyridin-2-one;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-hydroxy-ethyl)-N-methyl-benzamide;

methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-chlorobenzoate;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[3-(morpholine-4-carbonyl)-benzyl]-1H-pyridin-2-one;

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N,N-bis-(2-hydroxy-ethyl)-benzamide;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzoic acid methyl ester;

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-hydroxy-benzamide;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-hydroxymethyl-benzyl)-6-methyl-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-fluoro-benzyl)-1H-pyridin-2-one;

N-{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-methanesulfonamide;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[3-(pyrrolidine-1-carbonyl)-benzyl]-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one;

N-(3-aminopropyl)-3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide hydrochloride;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-methylaminomethyl-benzyl)-1H-pyridin-2-one;

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3,5-dichlorobenzenesulfonamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(dimethylamino)-2,6-difluorophenyl]-6-methylpyridin-2(1*H*)-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(4-piperidin-1-ylmethyl-benzyl)-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one;

N-(2-aminoethyl)-3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide hydrochloride;

3-bromo-1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one;

3-chloro-1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)-4-methylbenzamide;

2-{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-acetamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1*H*)-one hydrochloride;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzoic acid methyl ester;

1-(3-Aminomethyl-2-fluoro-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(morpholin-4-ylmethyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(4-fluorobenzyl)pyridin-2(1*H*)-

one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1*H*-indol-5-ylmethyl)pyridin-2(1*H*)-one;

1-[3-(aminomethyl)benzyl]-3-bromo-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one trifluoroacetate;

1-[3-(2-aminoethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one trifluoroacetate;

1-[3-(aminomethyl)benzyl]-3-bromo-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)benzamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-methoxy-benzyl)-6-methyl-1H-pyridin-2-one;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N,N-dimethyl-benzamide;

3-bromo-6-methyl-1-(pyridin-4-ylmethyl)-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1*H*)-one;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzamide;

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-methyl-benzamide;

{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-carbamic acid methyl ester;

3-bromo-4-[(2,6-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1*H*)-one;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzonitrile;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-

4-ylmethyl)pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3-bromo-6-methylpyridin-2(1*H*)-one;

1-Benzyl-4-benzyloxy-3-bromo-6-methyl-1H-pyridin-2-one;

1-benzyl-4-(benzyloxy)-3-bromo-6-methylpyridin-2(1*H*)-one;

1-Benzyl-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one;

{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-acetonitrile;

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-hydroxy-ethyl)-benzamide;

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-(3-fluoro-benzyl)-1H-pyridin-2-one;

1-Allyl-3-chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one;

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-[4-(isopropylamino-methyl)-benzyl]-1H-pyridin-2-one;

methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoate;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1*H*)-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(4-piperazin-1-ylmethyl-benzyl)-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1*H*)-one;

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N,N-dimethyl-benzamide;

3-bromo-1-(3-fluorobenzyl)-4-[(3-methylbenzyl)oxy]pyridin-2(1*H*)-one;

3-Bromo-1-(3-fluoro-benzyl)-4-(3-methyl-benzyloxy)-1H-pyridin-2-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1,2,3,4-tetrahydroisoquinolin-5-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-[(3-methylbenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(isoquinolin-5-ylmethyl)pyridin-2(1*H*)-one trifluoroacetate;

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyridin-2(1*H*)-one trifluoroacetate;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one;

1-allyl-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1*H*)-one;

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzamide;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1*H*)-one;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzoic acid;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(4-morpholin-4-ylmethyl-benzyl)-1H-pyridin-2-one;

4-(2,4-Difluoro-benzyloxy)-1-(3-fluoro-benzyl)-3-iodo-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-

trifluorophenyl)pyridin-2(1*H*)-one;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxybenzamide;

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,6-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzonitrile;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(pyrrolidin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-fluorobenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(4-methylbenzyl)pyridin-2(1*H*)-one;

3-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile;

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-isopropyl-benzamide;

3-bromo-1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(4-chlorobenzyl)pyridin-2(1*H*)-one;

4-Benzyloxy-3-bromo-1-(4-chloro-benzyl)-1H-pyridin-2-one;

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-Bromo-1-(4-fluoro-benzyl)-4-(4-fluoro-benzyloxy)-1H-pyridin-2-one;

methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoate;

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid;

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoic acid;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(2-fluorobenzyl)pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1*H*)-one;

N-(2-aminoethyl)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide hydrochloride;

4-Benzyloxy-3-bromo-1-(4-methylsulfanyl-benzyl)-1H-pyridin-2-one;

1-Benzyl-4-benzyloxy-3-chloro-1H-pyridin-2-one;

4-(benzyloxy)-3-bromo-1-[4-(methylthio)benzyl]pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3-chloropyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one;

3-bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[3-(isopropylamino-methyl)-benzyl]-1H-pyridin-2-one;

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-2-fluoro-benzamide;

5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*-(2,3-dihydroxypropyl)pyrazine-2-carboxamide;

{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-acetic acid ethyl ester;

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-N-hydroxy-benzamidine;

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}-*N'*-hydroxybenzenecarboximidamide;

ethyl 5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}pyrazine-2-carboxylate;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-methoxy-benzyl)-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-methoxybenzyl)pyridin-2(1*H*)-one;

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-dimethylaminomethyl-benzyl)-1H-pyridin-2-one;

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-(3-methanesulfonyl-benzyl)-1H-pyridin-2-one;

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester;

methyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoate;

ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}pyrazine-2-carboxylate;

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile;

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-

benzonitrile;

{3-[3-Bromo-4-(4-fluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-carbamic acid tert-butylester;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(1-hydroxy-1-methylethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1*H*)-one;

1-(3-Aminomethyl-benzyl)-4-benzyloxy-3-bromo-1H-pyridin-2-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(4-bromobenzyl)pyridin-2(1*H*)-one;

4-Benzyloxy-3-bromo-1-(4-bromo-benzyl)-1H-pyridin-2-one;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one;

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(piperazin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one hydrochloride;

3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1*H*)-one;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-Bromo-1-(3-fluoro-benzyl)-4-(4-fluoro-benzyloxy)-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one;

3-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester;

3-bromo-1-(3-fluorobenzyl)-4-{[2-(hydroxymethyl)benzyl]oxy}pyridin-2(1*H*)-one;

3-Bromo-1-(3-fluoro-benzyl)-4-(2-hydroxymethyl-benzyloxy)-1H-pyridin-2-one;

1-Benzo[1,3]dioxol-5-ylmethyl-3-bromo-4-(2,4-difluoro-benzyloxy)-1H-pyridin-2-one;

3-bromo-4-[(2,6-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-4-[(3-chlorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(3-chlorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

3-Bromo-4-(3-chloro-benzyloxy)-1-(3-fluoro-benzyl)-1H-pyridin-2-one;

4-(benzyloxy)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

4-Benzyloxy-3-bromo-1-(3-fluoro-benzyl)-1H-pyridin-2-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[3-(piperidine-1-carbonyl)-benzyl]-1H-pyridin-2-one;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*-dimethylbenzamide;

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-2-fluoro-benzoic acid methyl ester;

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1*H*)-one;

1-(3-Fluoro-benzyl)-4-(4-fluoro-benzyloxy)-3-iodo-1H-pyridin-2-one;

N-(3-aminopropyl)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-

6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide hydrochloride;

4-{[3-bromo-4-[(4-fluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile;

4-[3-Bromo-4-(4-fluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzonitrile;

3-Bromo-1-(3-fluoro-benzyl)-4-(2,3,4-trifluoro-benzyloxy)-1H-pyridin-2-one;

1-benzyl-4-(benzyloxy)-3-bromopyridin-2(1*H*)-one;

5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*-(2-hydroxyethyl)-*N*-methylpyrazine-2-carboxamide;

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzonitrile;

3-bromo-1-(2,4-difluorobenzyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-Bromo-1-(2,4-difluoro-benzyl)-4-(2,4-difluoro-benzyloxy)-1H-pyridin-2-one;

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)benzamide;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one;

1-Benzyl-4-benzyloxy-3-bromo-1H-pyridin-2-one;

3-bromo-1-(cyclopropylmethyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-(4-Aminomethyl-benzyl)-4-benzyloxy-3-bromo-1H-pyridin-2-one;

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1*H*)-one;

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzoic acid methyl ester;

5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*,*N*-dimethylpyrazine-2-

carboxamide;

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1*H*)-one;

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-1-(4-bromobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-hydroxy-1-(4-hydroxybenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one;

1-benzyl-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(piperidin-3-ylmethyl)pyridin-2(1*H*)-one hydrochloride;

1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate;

4-(benzylamino)-1-(3-fluorobenzyl)-6-methyl-3-nitropyridin-2(1*H*)-one;

tert-butyl 4-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]piperazine-1-carboxylate;

ethyl [4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]acetate;

N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]benzenesulfonamide;

3-bromo-4-[(4-*tert*-butylbenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-1-phenylmethanesulfonamide;

1-(biphenyl-2-ylmethyl)-3-bromo-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

4-(biphenyl-2-ylmethoxy)-3-bromo-1-(3-

fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorophenyl)amino]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

4-anilino-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

methyl 4-{[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]amino}benzoate;

3-bromo-1-(3-fluorobenzyl)-4-[(3,4,5-trimethoxyphenyl)amino]pyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-[4-(4-fluorophenyl)piperazin-1-yl]pyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-(4-methylpiperazin-1-yl)pyridin-2(1*H*)-one trifluoroacetate;

N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-2,5-difluorobenzamide;

N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-2,4-difluorobenzamide;

3-bromo-1-(cyclohexylmethyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanoic acid;

N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-*N'*-(2,4-difluorophenyl)urea;

3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanamide;

4-(benzyloxy)-3-bromo-1-(3-morpholin-4-yl-3-oxopropyl)pyridin-2(1*H*)-one;

N-(3-aminopropyl)-3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanamide hydrochloride;

4-(benzyloxy)-3-bromo-1-(3-oxo-3-piperazin-1-ylpropyl)pyridin-2(1*H*)-one hydrochloride;

4-(benzyloxy)-3-bromo-1-(2-morpholin-4-ylethyl)pyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-{[4-fluoro-2-(trifluoromethyl)benzyl]amino}pyridin-2(1*H*)-one;

N-(2-aminoethyl)-3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanamide hydrochloride;

[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]acetic acid;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(tetrahydrofuran-2-ylmethyl)pyridin-2(1*H*)-one;

4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(tetrahydrofuran-2-ylmethyl)pyridin-2(1*H*)-one;

methyl 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridine-1(2*H*)-carboxylate;

1-allyl-3-(2,4-difluorobenzyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-1-(2,2-diethoxyethyl)pyridin-2(1*H*)-one;

methyl *N*-acetyl-3-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]alaninate;

benzyl *N*-acetyl-3-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]alaninate;

benzyl *N*-[(benzyloxy)carbonyl]-3-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]alaninate;

4-(benzyloxy)-1-(2-oxopropyl)pyridin-2(1*H*)-one;

5-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl}-5-methylimidazolidine-2,4-dione;

ethyl [4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]acetate;

2-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]acetamide;

1-benzyl-4-(benzyloxy)-3,5-dibromopyridin-2(1*H*)-one;

4-(benzyloxy)-1-ethylpyridin-2(1*H*)-one;

4-(benzyloxy)-1-(4-*tert*-butylbenzyl)pyridin-2(1*H*)-one;

4-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile;

tert-butyl 3-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-

yl]methyl}piperidine-1-carboxylate;

1,3-dibenzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one;

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl methanesulfonate;

4-(benzyloxy)-1-(4-bromobenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromopyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one;

1-benzyl-4-(1-naphthylmethoxy)pyridin-2(1*H*)-one;

1-benzyl-4-(benzylthio)-3,5-dibromopyridin-2(1*H*)-one;

1-benzyl-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-3-[(benzylamino)methyl]-4-(benzyloxy)pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3-{[(2-cyclohexylethyl)amino]methyl}pyridin-2(1*H*)-one;

1-benzyl-4-(benzylthio)-5-methylpyridin-2(1*H*)-one;

1-benzyl-3-bromo-6-methyl-2-oxo-1,2-dihydropyridin-4-yl methanesulfonate;

1-benzyl-3-bromo-6-methyl-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one;

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate;

1-benzyl-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-benzyl-3-bromo-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate;

4-phenoxy-1-{[2-(trimethylsilyl)ethoxy]methyl}pyridin-2(1*H*)-one;

1-benzyl-4-phenoxypyridin-2(1*H*)-one;

1-(4-methoxybenzyl)-4-phenoxypyridin-2(1*H*)-one;

3-bromo-4-hydroxy-1-(4-hydroxybenzyl)pyridin-2(1*H*)-one hydrochloride;

4-(benzyloxy)-3-bromo-1-(piperidin-3-ylmethyl)pyridin-2(1*H*)-one;

1-benzyl-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3,5-dibromopyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-[(*E*)-2-(4-fluorophenyl)vinyl]pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-2-oxo-1,2-dihydropyridine-3-carbaldehyde;

1-benzyl-4-(benzyloxy)pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)pyridin-2(1*H*)-one;

1-benzyl-4-(benzylthio)pyridin-2(1*H*)-one;

methyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]benzoate;

benzyl (5-nitro-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)acetate;

ethyl 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxo-2*H*-1,2'-bipyridine-5'-carboxylate;

4-(benzyloxy)-1-(4-methylbenzyl)pyridin-2(1*H*)-one;

[5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridin-3-yl]methyl carbamate;

4-(benzyloxy)-1-(4-chlorobenzyl)pyridin-2(1*H*)-one;

methyl (2*E*)-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]but-2-enoate;

4-(benzyloxy)-1-(2-fluorobenzyl)pyridin-2(1*H*)-one;

tert-butyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}piperidine-1-carboxylate;

4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(1,2-dihydroxyethyl)-6-methylpyridin-2(1*H*)-one;

1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one;

4-({[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)benzonitrile;

1-benzyl-4-(benzyloxy)-6-methylpyridin-2(1*H*)-one;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde oxime;

1-benzyl-4-(benzylthio)-3-methylpyridin-2(1*H*)-one;

1-benzyl-4-[(4-methylbenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3,5-dibromo-6-methylpyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3,5-dibromo-6-methylpyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-(1-phenylethoxy)pyridin-2(1*H*)-one;

4-(benzyloxy)-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one;

2-({[3-bromo-2-oxo-1-(pyridin-3-ylmethyl)-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzonitrile;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile;

4-(benzyloxy)-1-(3-fluorobenzyl)-3-(trifluoromethyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-oxiran-2-ylpyridin-2(1*H*)-one;

1-benzyl-4-[(3-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-4-[(3-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde;

tert-butyl 3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}piperidine-1-carboxylate;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-vinylpyridin-2(1*H*)-one;

4-(benzyloxy)-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one;

3-bromo-4-[(4-chlorobenzyl)oxy]-1-[2-(phenylthio)ethyl]pyridin-2(1*H*)-one;

3-Bromo-4-(4-chloro-benzyloxy)-1-(2-phenylsulfanyl-ethyl)-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-morpholin-4-ylethyl)pyridin-2(1*H*)-one;

4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one;

4-{[2-(Aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate;

4-(benzyloxy)-1-(4-fluorobenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-1-(4-fluorobenzyl)pyridin-2(1*H*)-one;

4-Benzyloxy-3-bromo-1-methanesulfonyl-1H-pyridin-2-one;

tert-butyl 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]piperidine-1-carboxylate;

1-benzyl-4-(benzyloxy)-3-vinylpyridin-2(1*H*)-one;

4-(benzyloxy)-1-[4-(methylthio)benzyl]pyridin-2(1*H*)-one;

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(2-methyl-4-methylamino-pyrimidin-5-ylmethyl)-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one;

4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-1-[4-(methylsulfonyl)benzyl]pyridin-2(1*H*)-

one;

4-Phenoxy-1H-pyridin-2-one;

1-benzyl-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

methyl 4-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl}benzoate;

4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one;

1-(3-fluorobenzyl)-4-(phenylethynyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(piperidin-4-ylmethyl)pyridin-2(1*H*)-one hydrochloride;

4-(benzyloxy)-3-bromo-1-(piperidin-4-ylmethyl)pyridin-2(1*H*)-one hydrochloride;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(methylthio)pyrimidin-4-yl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-piperidin-4-ylpyridin-2(1*H*)-one hydrochloride;

4-Benzyloxy-1-difluoromethyl-1H-pyridin-2-one;

4-Benzyloxy-3-bromo-1-(2-chloro-phenyl)-6-methyl-1H-pyridin-2-one;

3-Bromo-6-methyl-1-pyridin-3-ylmethyl-4-[(pyridin-3-ylmethyl)-amino]-1H-pyridin-2-one;

1-(3,4-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2,4-difluoro-phenyl)-amide;

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2,4-difluoro-phenyl)-amide;

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2,4-difluoro-phenyl)-amide;

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl-phenyl-amide;

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid benzylamide;

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide;

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;

N-[5-Acetyl-1-(4-chloro-benzyl)-6-methyl-2-oxo-1,2-dihydro-pyridin-3-yl]-4-chloro-benzamide;

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid N'-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-hydrazide;

N-allyl-2-[(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)carbonyl]hydrazinecarbothioamide;

1-Benzyl-5-[5-(3,4-dichloro-benzylsulfanyl)-[1,3,4]oxadiazol-2-yl]-1H-pyridin-2-one;

N'-{[(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)carbonyl]oxy}pyridine-4-carboximidamide;

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 3-trifluoromethyl-benzylamide;

1-Benzyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;

5-[4-(3-Chloro-phenyl)-piperazine-1-carbonyl]-1-(3,4-dichloro-benzyl)-1H-pyridin-2-one;

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid benzylamide;

1-(4-Chloro-benzyl)-5-[3-(4-chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-1H-pyridin-2-one;

1-(4-Chloro-benzyl)-5-[3-(4-chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-1H-pyridin-2-one;

2-Chloro-N-[1-(2,6-dichloro-benzyl)-6-oxo-5-trifluoromethyl-1,6-dihydro-pyridin-3-yl]-4-fluoro-benzamide;

N-[1-(2,6-Dichloro-benzyl)-6-oxo-5-trifluoromethyl-1,6-dihydro-pyridin-3-yl]-4-isopropoxy-benzamidE;

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-

carboxylic acid (4-trifluoromethoxy-phenyl)-amide;

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-trifluoromethyl-phenyl)-amide;

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-trifluoromethyl-phenyl)-amide;

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (4-chloro-phenyl)-amide;

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2-dimethylamino-ethyl)-amide;

5-Methyl-1-phenyl-1H-pyridin-2-one;

3-Bromo-1-(3-fluoro-benzyl)-4-(3-methoxy-phenyl)-1H-pyridin-2-one;

3-Bromo-1-(3-fluoro-benzyl)-4-(3-isopropyl-phenyl)-1H-pyridin-2-one;

3'-Bromo-1'-(3-fluoro-benzyl)-6-methoxy-1'H-[3,4']bipyridinyl-2'-one;

4-Benzo[1,3]dioxol-5-yl-3-bromo-1-(3-fluoro-benzyl)-1H-pyridin-2-one;

3-Bromo-1-(3-fluoro-benzyl)-4-thiophen-3-yl-1H-pyridin-2-one;

3-Bromo-1-(3-fluoro-benzyl)-4-(3-trifluoromethyl-phenyl)-1H-pyridin-2-one;

3-Bromo-1-(3-fluoro-benzyl)-4-naphthalen-2-yl-1H-pyridin-2-one;

3-Bromo-1-(3-fluoro-benzyl)-4-(4-fluoro-phenyl)-1H-pyridin-2-one;

1-Benzenesulfonyl-4-benzyloxy-3-bromo-1H-pyridin-2-one;

4-[3-Amino-1-(2,4-difluoro-phenyl)-propoxy]-3-bromo-6-methyl-1-pyridin-3-ylmethyl-1H-pyridin-2-one;

1-(4-Bromo-2,6-difluoro-phenyl)-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one;

2-[1-(4-Amino-2-methyl-pyrimidin-5-ylmethyl)-3-bromo-6-

methyl-2-oxo-1,2-dihydro-pyridin-4-yloxymethyl]-5-fluoro-benzonitrile;

4-(2,4-Difluoro-benzyloxy)-6-methyl-1-(2,4,6-trifluoro-phenyl)-1H-pyridin-2-one;

1-(2-Chloro-4-hydroxy-phenyl)-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one;

3-[4-(2,4-Difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-benzoic acid methyl ester;

3-Bromo-1-(2,6-difluoro-phenyl)-4-methoxy-6-methyl-5-vinyl-1H-pyridin-2-one;

3-Bromo-1-(2,6-difluoro-phenyl)-4-methoxy-6-methyl-5-styryl-1H-pyridin-2-one;

1-(2,6-Difluoro-phenyl)-4-methoxy-6-methyl-5-phenethyl-1H-pyridin-2-one;

3-Bromo-1-(2,6-difluoro-phenyl)-4-methoxy-6-methyl-5-phenethyl-1H-pyridin-2-one;

1-(1*H*-indazol-5-yl)-4-(1*H*-indazol-5-ylamino)-6-methylpyridin-2(1*H*)-one;

5-Bromo-4-(2,4-difluoro-benzyloxy)-1-(2,6-difluoro-phenyl)-2-[2-(2,4-difluoro-phenyl)-ethyl]-6-oxo-1,6-dihydro-pyridine-3-carbaldehyde;

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-pyrimidine-2-carbonitrile;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid;

3-Bromo-4-(5-carboxy-pyridin-2-yloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6,6'-dimethyl-2-oxo-2H-[1,2']bipyridinyl-3'-carbonitrile;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid methylamide;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-

[1,2']bipyridinyl-5'-carboxylic acid (2-hydroxy-ethyl)-amide;

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid (2-methoxy-ethyl)-amide;

3-Bromo-1-(2,6-difluoro-phenyl)-4-methoxy-6-methyl-5-(4-methyl-benzyl)-1H-pyridin-2-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(1,2-dihydroxy-2-phenylethyl)-6-methylpyridin-2(1H)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-5'-(1-hydroxy-1-methylethyl)-6-methyl-2H-1,2'-bipyridin-2-one;

4-Benzyloxy-1H-pyridin-2-one;

4-Benzyloxy-3-methyl-1H-pyridin-2-one;

2-Oxo-6-phenethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-Oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile;

6-Oxo-1,6-dihydro-[2,3']bipyridinyl-5-carbonitrile;

6-Oxo-1,6-dihydro-[2,3']bipyridinyl-5-carboxylic acid;

3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzamide;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-5-(hydroxymethyl)phenyl]-6-methylpyridin-2(1*H*)-one;

3-chloro-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-chloro-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(3-chlorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-4-[(3,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoic acid;

3-bromo-1-(3-chlorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(3-chlorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

4-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile trifluoroacetate;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(1-hydroxy-1-methylethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one;

4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-6-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1*H*)-one trifluoroacetate;

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-methylbenzamide;

1-[2-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

1-[2-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(piperidin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)-3-

methylpyridin-2(1*H*)-one;

4-(benzyloxy)-1-[4-(benzyloxy)benzyl]-3-bromopyridin-2(1*H*)-one;

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxybenzamide;

4-(benzyloxy)-1-[4-(benzyloxy)benzyl]-3-bromopyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one;

3-bromo-1-(cyclopropylmethyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(cyclopropylmethyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyridin-2(1*H*)-one trifluoroacetate;

3-bromo-1-(3-fluorobenzyl)-4-[(2-methylbenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-[(2-methylbenzyl)oxy]pyridin-2(1*H*)-one;

methyl 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzoate;

3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-[(4-methylbenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-[(4-methylbenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-[(4-methylbenzyl)oxy]pyridin-2(1*H*)-one;

4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1*H*)-one;

3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzoic acid;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-[2-(hydroxymethyl)benzyl]pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(5-{[(2-hydroxyethyl)(methyl)amino]methyl}pyrazin-2-yl)methyl]-6-methylpyridin-2(1*H*)-one trifluoroacetate (salt);

4-(benzyloxy)-3-bromo-1-[(6-fluoropyridin-3-yl)methyl]pyridin-2(1*H*)-one;

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(4-chloro-2-fluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one;

2-(2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}phenyl)acetamide;

1-benzyl-3-bromo-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

methyl 2-{[3-bromo-4-[(4-fluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzoate;

3-bromo-1-(2,6-dichlorophenyl)-4-[2-(4-fluorophenyl)ethyl]-6-methylpyridin-2(1*H*)-one;

3-bromo-1-(2,6-dichlorophenyl)-4-[2-(4-fluorophenyl)ethyl]-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{5-[(isopropylamino)methyl]-2-methylphenyl}-6-methylpyridin-2(1*H*)-one hydrochloride;

3-bromo-1-(3-fluorobenzyl)-4-(2-phenylethyl)pyridin-2(1*H*)-one;

N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}-*N*'-methylurea;

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-[(3-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[2-(2-thienyl)ethyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[2-(2-thienyl)ethyl]pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one trifluoroacetate;

3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one trifluoroacetate;

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one;

3-bromo-1-(4-chlorobenzyl)-4-[(4-

chlorobenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-[(4-methoxybenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(3,5-dibromo-2,6-difluoro-4-hydroxyphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one;

N'-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}-*N*,*N*-dimethylurea;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one;

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide;

N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}morpholine-4-carboxamide;

N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}methanesulfonamide;

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-isopropylbenzamide;

4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one;

4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one;

(4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}phenyl)acetic acid;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(pyrrolidin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-3-iodopyridin-2(1*H*)-one;

1-(biphenyl-4-ylmethyl)-3-bromo-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoic acid;

4-(benzyloxy)-3-bromo-1-[2-(3-thienyl)ethyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-[2-(3-thienyl)ethyl]pyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-[3-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one;

N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-4-fluorobenzamide;

methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzylcarbamate;

1-benzyl-4-(benzylthio)-3-bromopyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(4-*tert*-butylbenzyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-(4-*tert*-butylbenzyl)pyridin-2(1*H*)-one;

N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}-2-methoxyacetamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-({5-[(dimethylamino)methyl]pyrazin-2-yl}methyl)-6-methylpyridin-2(1*H*)-one trifluoroacetate;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(piperazin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one hydrochloride;

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*-bis(2-hydroxyethyl)benzamide;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{5-[(dimethylamino)methyl]-2-methylphenyl}-6-methylpyridin-2(1*H*)-one hydrochloride;

1-benzyl-3-bromo-4-(2-phenylethyl)pyridin-2(1*H*)-one;

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-

methylpyridin-2(1*H*)-one;

4-(benzyloxy)-1-(piperidin-3-ylmethyl)pyridin-2(1*H*)-one trifluoroacetate;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-1-(3-fluorobenzyl)-3-methylpyridin-2(1*H*)-one;

N^1-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}glycinamide hydrochloride;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(piperidin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one;

N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-2,6-difluorobenzamide;

2-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile;

5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*-methylpyrazine-2-carboxamide;

3-chloro-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one;

3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoic acid;

3-bromo-1-(3-fluorobenzyl)-4-[(3-fluorobenzyl)amino]pyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-[(3-methoxybenzyl)oxy]pyridin-2(1*H*)-one;

3-bromo-1-(4-*tert*-butylbenzyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one;

N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}acetamide;

2-({3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

oxopyridin-1(2*H*)-yl]benzyl}amino)-2-oxoethyl acetate;

1-benzyl-4-(benzyloxy)-3-methylpyridin-2(1*H*)-one;

N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}urea;

1-benzyl-4-(benzyloxy)-3-ethylpyridin-2(1*H*)-one;

N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}-2-hydroxyacetamide;

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(2-phenylethyl)pyridin-2(1*H*)-one;

3-bromo-1-(3-chlorobenzyl)-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one;

1-[3-(aminomethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one;

2-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzamide;

1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

1-[2-(aminomethyl)benzyl]-4-(benzyloxy)-3-bromopyridin-2(1*H*)-one;

methyl 3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanoate;

1-benzyl-4-(benzyloxy)-3-methylpyridin-2(1*H*)-one;

4-(allylamino)-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one;

4-(allylamino)-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-(phenylethynyl)pyridin-2(1*H*)-one;

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*-dimethylbenzamide;

{4-[({4-(benzyloxy)-3-bromo-1-[4-(carboxymethyl)benzyl]-1,2-dihydropyridin-2-yl}oxy)methyl]phenyl}acetic acid;

4-(benzyloxy)-3-bromo-1-[3-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one;

4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{3-[(dimethylamino)methyl]phenyl}-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one;

1-benzyl-3-bromo-4-(phenylethynyl)pyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one;

3-bromo-1-(3-fluorobenzyl)-4-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one;

4-(benzylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one;

4-[(2,4-difluorobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2(1*H*)-one;

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one hydrobromide;

4-(benzyloxy)-3-bromo-1-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid;

1-benzyl-3-bromo-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one;

3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-methylbenzoic acid;

4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]benzoic acid;

ethyl *N*-(5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-2-methylpyrimidin-4-yl)glycinate trifluoroacetate;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-[(*E*)-2-phenylvinyl]pyridin-2(1*H*)-

one;

3-bromo-1-(3-fluorobenzyl)-4-{[3-(trifluoromethyl)benzyl]amino}pyridin-2(1*H*)-one;

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(3-phenylpropyl)pyridin-2(1*H*)-one;

3-bromo-1-(4-*tert*-butylbenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one;

4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one;

1-cyclohexyl-4-[(2,4-difluorobenzyl)oxy]-3,6-dimethylpyridin-2(1*H*)-one;

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(hydroxymethyl)-6-methylpyridin-2(1*H*)-one;

1-benzyl-4-(benzyloxy)-2-oxo-1,2-dihydropyridine-3-carbaldehyde;

4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-prop-2-yn-1-ylpyridin-2(1*H*)-one;

ethyl 3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanoate;

1-benzyl-4-(benzyloxy)-3-(hydroxymethyl)pyridin-2(1*H*)-one;

3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(5-methyl-pyrazin-2-ylmethyl)-1H-pyridin-2-one

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-(5-hydroxymethyl-pyrazin-2-ylmethyl)-6-methyl-1H-pyridin-2-one

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(2,3-dihydro-1H-indol-5-ylmethyl)-1H-pyridin-2-one

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[1-(2-hydroxy-acetyl)-2,3-dihydro-1H-indol-5-ylmethyl]-6-methyl-1H-pyridin-2-one

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(1H-pyrazol-3-ylmethyl)-1H-pyridin-2-one

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-4,N-dimethyl-benzamide

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-4-methyl-benzamide

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-4-fluoro-N-methyl-benzamide

4-Chloro-3-[3-chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-N-methyl-benzamide

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-4-fluoro-benzamide

4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-3,N-dimethyl-benzamide

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-[4-(1,2-dihydroxy-ethyl)-2-methyl-phenyl]-6-methyl-1H-pyridin-2-one

N-{4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-2-hydroxy-acetamide

1-Hydroxy-cyclopropanecarboxylic acid 4-[3-chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzylamide

N-{4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-2-hydroxy-acetamide

N-{4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-acetamide

{2-[3-Bromo-1-(2,6-difluoro-phenyl)-6-methyl-2-oxo-1,2-dihydro-pyridin-4-yloxymethyl]-5-fluoro-benzyl}-carbamic acid ethyl ester; or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Internal application No
PCT/US 03/04634

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4412 A61P29/00 C07D213/69 C07D401/06 C07D409/06
C07D213/70 C07D213/64 C07D213/74 C07D405/06 C07D213/84
C07D401/10 C07D405/12 C07D401/12 C07D213/75 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 10712 A (MARGOLIN SOLOMON B) 27 March 1997 (1997-03-27) page 37, line 7 - line 16; claims 1,2,4 ---	1-74
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X	US 3 654 291 A (GRAHAM PATRICIA M ET AL) 4 April 1972 (1972-04-04) column 2, line 33 -column 3, line 29; examples 5-29 ---	1-74
X	GB 1 289 187 A (MERCK & CO INC) 13 September 1972 (1972-09-13) examples claims 1,21,30 --- -/--	1-74

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2003	23/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seymour, L

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 03/04634

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/79 C07D401/04 C07D405/04 C07D413/10 C07D215/22
C07D405/14 C07D409/14 C07D213/85

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 644 626 A (WITZEL BRUCE E) 22 February 1972 (1972-02-22) the whole document ---	1-74
X	WO 00 31063 A (CRICH JOYCE Z;ANANTANARAYAN ASHOK ; CLARE MICHAEL (US); SEARLE & C) 2 June 2000 (2000-06-02) page 262; claim 1 page 1, line 11 - line 13 --- -/--	1,68

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Seymour, L

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 5069110 (BRN) XP002243098 & JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, 1986, pages 1289-1296, ---	1,36
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 5587856 (BRN) XP002243099 see also Product BRN 7719203 & LIEBIGS ANN., RECL., vol. 8, 1997, pages 1777-1782, ---	1,36
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 6347000 (BRN) XP002243100 & COLLECT. CZECH. CHEM. COMMUN., vol. 58, no. 4, 1993, pages 947-953, ---	1,36
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X	WO 86 01815 A (SANDOZ AG) 27 March 1986 (1986-03-27) claim 6, formula IIIa starting material for Ex. No. 81 -----	1,36

INTERNATIONAL SEARCH REPORT

Inte ›nal application No.
PCT/US 03/04634

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 68 and 69 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to compounds according to claim 36.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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